United States Court of Appeals

for the Second Circuit

JOINT APPENDIX

76-6135

In The

United States Court of Appeals

For The Second Circuit

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR, CO., INC.,

Plaintiffs-Appellants,

vs.

F. DAVID MATHEWS, Secretary of Health, Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants-Appellees.

On Appeal from the United States District Court for the Southern District of New York.

JOINT APPENDIX

Volume II, 315a - End

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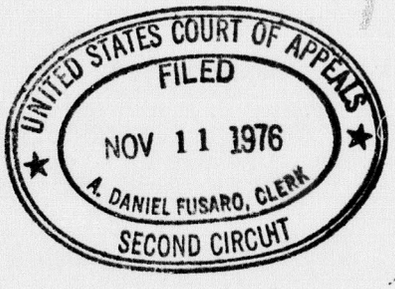

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age levels be sold only upon prescription could in that event hardly be labelled arbitrary, capricious or contrary to law.

[19] We reject petitioners' contention that because the higher dosage levels are not "inherently" unsafe but become unsafe only if used in violation of cautionary labelling they do not qualify as "prescription" drugs within the meaning of § 503(b) of the Act, 21 U.S.C. § 353(b). The broad language of § 503(b)(1)(B) [13] permits consideration of the various factors surrounding the use of a particular drug in determining that it "is not safe for use except under the supervision of" a physician. There was ample evidence before the FDA that Vitamins A and D, when consumed in large quantities over a period of time, can be acutely toxic. It was reasonable for the Commissioner to recognize that the risks of toxicity are increased by over-the-counter availability of readily ingestible, high dosage forms, and therefore he could rationally conclude that these forms have a "potential harmful effect."

The appellants' arguments that the Commissioner's determination is irrational because high concentrations of Vitamins A and D also occur in natural foods, use of which is not restricted, and because the Commissioner's rationale would also require drugs like aspirin to be placed on a prescription basis, must also be rejected. Although some ordinary foods contain potent doses of Vitamins A and D, there is no indication that these foods are consumed on the same regular basis as the easily ingestible pills. Indeed, the fact that many persons obtain significant quantities of these vitamins from ordinary foods increases the risks of toxicity from regular consumption of high dosage pill forms. Likewise, although consumption of aspirin in excessive quantities presents risks of toxicity, there is no evidence that aspirin is consumed on the same regular basis as vitamins. The FDA here was not confronted with a case in which there was the mere possibility that a drug would be occasionally misused, but one in which the actual way in which the product is apparently used on a normal basis by many persons presents serious risks of toxicity. The Commissioner's action in classifying the higher dosage forms as "prescription drugs" thus cannot be called irrational or arbitrary.[14]

If, however, the district court concludes on remand that the Commissioner's treatment of the higher dosage forms as "drugs" under the § 201(g) definition, based on the record before the Commissioner, is irrational, then the order granting summary judgment must be vacated.

The case is remanded to the district court for further proceedings not inconsistent with the foregoing.

LUMBARD, Circuit Judge (concurring):

I am not as confident as my brothers that Congress intended the FDA to have substantive rule-making authority with respect to the prescription status of drugs. However, in light of the bare statutory language of section 701(a), 21 U.S.C. § 371(a), the lack of clear legisla-

13. See fn. 3 *supra*.

14. Appellants urge the decision in United States v. An Article of Drug— Decholin, 264 F.Supp. 473 (E.D.Mich.1967) as support for their position that the higher dosage form vitamins cannot be classified as prescription drugs. That case involved an effort by the Government to classify Decholin as a prescription drug because there was a possibility that if used in certain ways it could harm. The *Decholin* case is not in point however since there had been no proof at all of toxicity. Here, the appellants do not contest the findings of Vitamin A and D toxicity at least at very high levels. Moreover, in *Decholin* the court states:

> "[T]he Government itself all but concedes that if future unadvised laymen act as their predecessors have, the drug will not be responsible for any serious consequences. . . . [W]hile in theory Decholin may be harmful as an over-the-counter drug, in practice it is safe for use without prescription." 264 F.Supp. at 478.

In our case, the Government takes just the reverse position—although higher dosage vitamin tablets may theoretically be safe if used as directed, they are in practice not safe for use without a prescription.

tive history denying such power to the FDA, and recent judicial trends, see, e. g., Mourning v. Family Publication Services, Inc., 411 U.S. 356, 93 S.Ct. 1652, 36 L.Ed.2d 318 (1973); National Petroleum Refiners Assn. v. FTC, 157 U.S.App. D.C. 83, 482 F.2d 672 (1973), cert. denied; 415 U.S. 951, 94 S.Ct. 1475, 39 L.Ed.2d 567 (1974), there seems little doubt that these regulations would be upheld by the Supreme Court.

What motivates this brief concurring statement is my concern that substantive agency action receive adequate review in the courts. What Congress intended in 1938, when the FDA was created, is less than clear with respect to the exercise of substantive rule-making powers under such a provision as section 701(a). However, in light of the fact that the FDA did not choose to exercise such power for so many years after it was supposedly granted, it would be less than realistic to think that Congress gave such rule-making much thought when it passed the Administrative Procedure Act in 1946.[1] Consequently, the quality and nature of judicial review of such rule-making as occurred here is open to some speculation.

As Judge Mansfield points out, the Administrative Procedure Act provides that the proper scope of review here is whether the agency action was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This is so despite the fact that Congress provided a different form of review—one which required the FDA's actions to be based on substantial evidence—when it specifically authorized the FDA to engage in substantive rule-making. *See* 21 U.S.C. § 371(e), (f).

Courts have chosen to uphold ever more generously and liberally the exercise of substantive rule-making powers by administrative agencies. Consequently it seems to me only appropriate that when courts approve such broader powers, they give due consideration to whether analogous changes may be needed in judicial interpretation of the Administrative Procedure Act. In cases such as this, where an agency engages in substantive rule-making under the authority of a general rule-making authorization, the courts should interpret the phrase "arbitrary, capricious, [or] an abuse of discretion" so as to ensure that real judicial review of agency action is provided. A district judge should carefully examine the information that was before the agency to see if it gives adequate and substantive support to the agency's position.[2] While a court should not substitute its views for those of the agency, it should not think that the "arbitrary [or] capricious" standard is so loose that it must approve anything that an agency does so long as the agency's actions are not completely irrational. Indeed, in the area of substantive rule-making a court should not hesitate to overturn an agency's action if it is not fairly supported by the evidence before the agency. In essence I think that when an agency engages in substantive rule-making, it abuses its discretion (or acts arbitrarily or capriciously) if its actions are not supported by substantial evidence. Cf. 5 U.S.C. § 706(2)(E).

Although Judge Frankel applied the traditional "arbitrary [or] capricious" standard of review in this case, an examination of the language of his two opinions on these regulations suggests to me that he did conduct a review similar to what I espouse here. Indeed, at one point he states that he probably would have reached the same conclusion as the FDA did on a particular issue if he had initially been called to rule on it.

For these reasons, I concur.

1. Another example of an agency recently deciding that a long-standing statute authorized the issuance of substantive rules is provided by National Petroleum Refiners Assn. v. FTC, supra.

2. Section 4 of the Administrative Procedure Act, 5 U.S.C. § 553, requires that an agency give "a concise general statement of [the] basis and purpose" of rules that it adopts. As Judge Mansfield notes, an agency has an obligation to publish a statement of reasons that is sufficiently detailed to permit judicial review. Opinion at 701.

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

----------X

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC., :

Plaintiffs :

v. :

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs, :

Defendants :

73 Civ. 3448 MEF

AFFIDAVIT

----------X

County of Montgomery)
State of Maryland)

Alexander M. Schmidt, M.D., Commissioner of Food and Drugs, first being duly sworn, deposes and says:

(1) In the Federal Register of August 2, 1973, 38 F.R. 20723-20725, I promulgated final regulations for the United States Food and Drug Administration which provide that high dosage preparations of vitamins A and D, as specified in the regulations, are deemed to be prescription drugs. These regulations appear in Title 21 of the Code of Federal Regulations, Sections 3.94 and 3.95 (21 CFR 3.94 and 3.95). Copies of the notice of proposed rulemaking, a subsequent correction, and the final regulation, as published in the Federal Register, are attached.

(2) I have now read the decision of the United States Court of Appeals for the Second Circuit, captioned National Nutritional Foods Assn. v. Weinberger, Docket No. 74-1738, decided February 3, 1975, and it is my understanding that the Court of Appeals

has upheld our regulations in all but one respect, i.e., it has returned the case to the United States District Court for the Southern District of New York for specific inquiry into the basis on which I concluded that high dosage oral preparations of vitamins A and D are "drugs". My lawyers have advised me that I should accordingly explain in detail my basis for categorizing these products as drugs.

(3) At the outset, I want to make clear that I am familiar with the definition of the term "drug" contained in Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(g)(1), and that I believe the high dosage vitamin A and D products involved in these regulations come within this definition:

> The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

(4) Speaking frankly, I believe we did not set forth a more detailed rationale for the drug status of these high dosage preparations in the Federal Register of August 2, 1973, because we felt the classification was so obviously proper. When I promulgate a regulation concerning labeling or composition for articles which I know to be recognized in the United States Pharmacopeia and in the National Formulary, which are being sold in the form of pills and capsules, which I know -- from my experience as a

practicing physician and as a medical school dean and more recently as Commissioner of Food and Drugs -- are being widely prescribed by physicians for the treatment of serious disease conditions, and which are too potent and toxic to be useful for ordinary nutritional purposes, I simply do not pause for long over the issue of whether such articles are drugs. Similarly, if I were promulgating today a regulation concerning the labeling of an oral penicillin product, or a polio vaccine to be dispensed on a sugar cube, I would not seriously pause for long over some objection that such products were "foods". In any event, I shall now proceed to explain, to the best of my memory, why I concluded then, and would conclude now, that high potency vitamin A and D preparations are drugs.

(5) Section 201(g)(1)(B) of the Act, 21 U.S.C. 321(g)(1)(B), provides that the term "drug" includes "articles intended for use in the ... cure, mitigation, treatment, or prevention of disease ..." In National Nutritional Foods Assn. v. FDA, 504 F.2d 761, 789 (2d. Cir. 1974), Judge Friendly observed that under Section 201(g)(1)(B) an article may be deemed to be a drug, in spite of a manufacturer's "subjective" claims of other intent, if the "objective evidence" demonstrates therapeutic intent.

Pursuant to Judge Friendly's ruling, it seems to me that it is reasonable and proper for me to categorize high dosage preparations of vitamins A and D as drugs because these preparations, viewed objectively, are intended for therapeutic usage. Indeed, our notice of proposed rule making in the Federal Register specifically took note of "widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders".

I have long been aware of the numerous and widespread therapeutic usages for these products. For example, high dosages of vitamin A, exceeding 10,000 IU and ranging up to 100,000 IU per day, depending upon the condition, are used in the treatment of severe primary vitamin A deficiency and xerophthalmia, and of diseases and disorders which interfere with absorption of vitamin A, e.g., biliary cirrhosis of the liver, sprue, cystic fibrosis, infantile and adult celiac disease, and biliary obstruction. High dosages of vitamin A have also been used as an anti-infective agent for prevention of renal calculi, and in the treatment of acne, hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, and cutaneous ulcerative conditions -- although evidence is lacking to demonstrate efficacy for these usages.

High dosages of vitamin D, exceeding 400 IU and ranging up to 800,000 IU per day, depending upon the condition, are used in the treatment of, e.g., ordinary rickets, vitamin D resistant rickets, hypoparathyroidism, infantile tetany, a group of diseases characterized by intestinal malabsorption, e.g., severe gluten enteropathy, and diseases that affect the bone and kidneys, e.g., familial hypophosphatemias, the Fanconi syndrome, and chronic uremia. Large doses may be required in patients with successful kidney transplants. High dosages of vitamin D have also been used in the treatment of psoriasis, arthritis and hay fever (although the rationale of therapy for these last three usages is subject to serious question).

In any of these cases involving large doses of vitamins A or D, extreme care is required to adjust, and frequently readjust, doses to obtain maximal therapeutic benefit while keeping toxic effects as low as possible.

I am attaching to this affidavit a copy of the AMA Drug Evaluations, pages 153-159 (2nd ed. 1973) concerning vitamins A and D. This is a standard reference work to which physicians turn routinely, reflecting the basic understanding among the medical profession concerning various commonly used drugs, and it ably illustrates the variety of therapeutic usages, familiar to physicians, for which vitamin A and D preparations are used.

It seems to me that the seller of such a high potency vitamin A or D preparation, which exceeds the levels recognized to be useful for ordinary nutritional supplementation, knows or should know that his product is likely to be used by purchasers hoping for some therapeutic benefit such as deliverance from cirrhosis, acne, psoriasis or arthritis. Frankly, it makes no more sense to me that someone should be able to say that such a product is not a drug because he subjectively wants to eat it as a food than it would to allow distributors of aspirin or LSD to avoid regulation of their products as drugs by saying that they have some customers who like the taste and who subjectively choose to regard these articles as foods.

(6) Section 201(g)(1)(A) of the Act, 21 U.S.C. 321(g)(1)(A), provides that the term "drug" includes "articles recognized in the official United States Pharmacopeia ... or official National Formulary ..." Both vitamin A and vitamin D are recognized in the United States Pharmacopeia and in the National Formulary.

Monographs for vitamin A and vitamin A capsules appear in U.S. Pharmacopeia XVIII at pages 775-776, and an assay for vitamin A appears in the same text at pages 914-915 and in National Formulary XIII at pages 891-892. The term "vitamin D" refers to either of two sterols, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), that have equal antirachitic potency in man. Monographs for cholecalciferol and ergocalciferol appear in U.S. Pharmacopeia XVIII at pages 130-131, 231-232, while assays for vitamin D appear in U.S. Pharmacopeia XVIII at pages 915-917 and in National Formulary XIII at pages 895-899. The U.S. Pharmacopeia will provide reference standard samples of vitamins A and D for pharmaceutical analysis. See U.S. Pharmacopeia XVIII, pages 822-825. Copies of the foregoing documents are attached to my affidavit. U.S. Pharmacopeia XVIII and National Formulary XIII were in effect at the time of the promulgation of the regulations and are still in effect today.

I agree with Judge Friendly's statement in the case of National Nutritional Foods Association v. FDA, 504 F.2d 761, 789 (2d. Cir. 1974), that it "would prove too much" to say that all vitamin preparations are drugs simply because vitamins are recognized in the U.S. Pharmacopeia or the National Formulary. However, it is simply not necessary to reach Judge Friendly's reductio ad absurdum under which all vitamins and minerals might arguably be classified as drugs because they appear in an official compendium.

Unlike most articles recognized in the U.S. Pharmacopeia and the National Formulary, which are included because of therapeutic usage, vitamins are specifically recognized in the U.S.P. and N.F. for food usage as well as for therapeutic usage. In my judgment, while the Act provides that an

article is deemed to be a drug if "recognized" in the U.S.P. or N.F., a vitamin preparation should nevertheless not be classified as a drug on this basis with respect to a usage which is specifically recognized by these compendia to be a food usage.

Thus, 400 units of vitamin D is specifically recognized in the U.S. Pharmacopeia for "prophylactic" use, i.e., as a nutritional use for ordinary food purposes to maintain good health. Similarly, 5,000 units of vitamin A is recognized as the usual prophylactic daily quantity of vitamin A, with a usual range for this purpose of 4,000 to 8,000 units. In both instances, the therapeutic quantity is recognized to be higher. These recognized food usage levels of up to 400 units for vitamin D and 8,000 units for vitamin A do not overlap, and indeed are entirely consistent with, the levels adopted in our regulations as the base line for prescription drug status.

In sum, in the context of high potency vitamin A and D preparations, it does not seem to me to "prove too much" to say that such recognition in the United States Pharmacopeia and National Formulary is sufficient to confirm, if not to establish, their drug status. Such application of the language of 21 U.S.C. 321(g)(1)(A) would not result in all vitamin A and D preparations being "drugs".

Nor does it seem unreasonable for me as Commissioner of Food and Drugs, charged with the enforcement of the Federal Food, Drug, and Cosmetic Act, to take note that, in the absence of therapeutic claims, the "food" definition in 21 U.S.C. 321(f) fairly applies to lower dosages of vitamins A and D, which possess nutritional usefulness, and to decide that in view

of the existence of two definitions applicable to preparations of vitamins A and D, I will, in the interest of efficient enforcement of the law, restrict the drug definition (in the absence of therapeutic claims for a lower potency product) to high potency preparations which are inappropriate for nutritional use and which possess a real potential for human harm.

(7) I am aware of Judge Friendly's statement in National Nutritional Foods Assn. v. FDA, 504 F.2d 761, 789 (2d. Cir. 1974) (reviewing 21 CFR 125.1(h) and not the present vitamin A and D regulations) that "demonstrated uselessness as a food for most people" is not a sufficient basis for my declaring all such articles to be drugs. Whatever the merits of 21 CFR 125.1(h), it seems clear to me that much more than "demonstrated uselessness as a food for most people" is involved in the drug determination in the present vitamin A and D regulations. The situation is much more extreme. These high potency vitamin A and D preparations provide excessive amounts of the vitamins which are useless as a food for virtually anyone unless such person is suffering from a serious disease condition requiring continuing medical supervision, in which case carefully selected quantities of the vitamin(s) are used as part of the total therapy of the patient.

Furthermore, the levels involved in the vitamin A and D regulations pose a dangerous potential for harm. In promulgating these regulations, concern over the public harm that could be done by these high potency therapeutic preparations weighed more heavily upon my mind than any other single factor.

The notice of proposed rule making listed in considerable detail the various types of harm that people can do to themselves, or to their children, or to an unborn fetus, by overdosing with these vitamins. Among the

adverse effects from excessive intake of vitamin A to which our notice referred were: anorexia, growth retardation in children, drying and cracking of the skin, hepatosplenomegaly, increased intra-cranial pressure, alopecia, migratory arthralgia, bone pain, hypomenorrhea, irritability, and headache.

Noting that "[g]enerally, the margin of safety between nutritional requirements and toxic levels is small for vitamin D", we detailed the consequences of hypervitaminosis D:

> [A]norexia, nausea, weakness, weight loss, polyuria, constipation, vague aches, stiffness, generalized vascular, soft tissue and premature epiphyseal calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure and death.
>
> * * *
>
> There is good evidence suggesting that the supravalvular aortic stenosis syndrome with hypercalcemia in infants and children may result from excess intakes of vitamin D by the infant and/or by the mother during pregnancy. This latter syndrome may have a tragic outcome with severe aortic stenosis, mental and physical retardation, elfin facies, renal failure and death.

Indeed, I note that even the Court of Appeals apparently had no serious doubts about the potential for harm in view of the Court's statement at page 1620 of their opinion that:

> There was ample evidence before the FDA that Vitamins A and D, when consumed in large quantities over a period of time, can be acutely toxic. It was reasonable for the Commissioner to recognize that the risks of toxicity are increased by over-the-counter availability of readily ingestible, high dosage forms, and therefore he could rationally conclude that these forms have a "potential harmful effect."

In this regard, I call to the Court's attention that our judgment concerning the toxicity of vitamin D has very recently been reinforced among the scientific community by a special report on the "Hazards of Overuse of Vitamin D" issued by the Food and Nutrition Board of the National Academy of Sciences/National Research Council, published in Nutrition Reviews, vol. 33, no. 2, February 1975, pages 61-62. (Copy attached.) Among other things, this report concludes:

> ... excessive amounts of vitamin D are hazardous and only individuals with diseases affecting vitamin D absorption or metabolism require more than 400 IU per day. Such needs should be established by clinical evaluation, and treatment should be specifically recommended and supervised by physicians.

In sum, unlike the circumstances addressed by Judge Friendly, far more than "demonstrated uselessness as a food for most people" is involved here. In the case of these high potency vitamin A and D preparations, we have demonstrated uselessness as a food for virtually anyone not suffering from a serious disease or disorder requiring continuing medical supervision, as well as (1) a dangerous risk of harm to the public health, (2) widespread use for therapeutic purposes (see paragraph 5 of this affidavit) and (3) recognition in the United States Pharmacopeia and in the National Formulary (see paragraph 6 of this affidavit).

(8) Of course, explicit therapeutic claims made for a product in its labeling, advertising, etc., would cause an article to be deemed a drug regardless of its actual potency. 21 U.S.C. 321(g)(1)(B).

(9) In addition to protection of the public from the toxic effects of overdosing, classification of these high potency products as drugs (and consequently, because of their potential for harm, as prescription drugs) would redound in other ways to the benefit of the public health. For example:

(a) Our Food and Drug Inspectors, upon conducting a factory inspection, are entitled to demand production of master formula records, batch production records, reports of analyses and other quality control records if these products are prescription drugs, but not if the products are foods. 21 U.S.C. 374(a). Such records are very helpful in assuring, e.g., that potent ingredients are evenly dispersed, in the labeled amount, throughout a batch of tablets.

(b) Persons who produce drugs must register their names and addresses with the Food and Drug Administration on a yearly basis, which facilitates our regular inspection of all such persons; persons who deal in foods are not subject to this requirement. 21 U.S.C. 360.

(c) If drugs, these products are subject to detailed drug good manufacturing practice ("GMP") regulations, which address directly the type of manufacture involved in the production of vitamin preparations, 21 U.S.C. 351(a)(2)(B), 21 CFR 133.2-133.15, while if foods they are subject to the more general food GMP regulations which are not designed to provide the same precision of control of ingredients. 21 CFR 128.

(10) Moreover, it would serve no useful purpose to recognize in the regulations a hypothetical food use of such high dosage oral preparations of vitmins A and D because any such food use would be illegal. The Court of Appeals has already recognized that, if classified as drugs, these high dosage oral preparations pose such a potentiality for public harm that the Food and Drug Administration may properly restrict their availability to prescription sale. Since such a potential for harm exists, such a high potency of vitamin A or D would lack general recognition of safety for inclusion as a component in a preparation intended for over-the-counter sale as a food to laymen, and would thus be a food additive within the meaning of 21 U.S.C. 321(s). Since there is no exemption or regulation permitting such food additive use, such a food additive usage would be deemed to be ussafe pursuant to 21 U.S.C. 348(a) and the finished preparation would accordingly be deemed to be adulterated pursuant to 21 U.S.C. 342(a)(2)(C). Surely any rational person would agree that a potent ingredient which causes a preparation not to be safe for use except under the supervision of a physician, and which thus causes the preparation to be a prescription drug if classified as a drug, would of necessity lack general recognition of safety for inclusion in a food preparation intended for sale in grocery stores, and would thus be deemed a food additive for any such food use within the meaning of 21 U.S.C. 321(s). In sum, it appears to me that there would be no point in recognizing in the regulation a hypothetical food usage which would be illegal; indeed, the illegality of any such food usage is implicit and inherent in the issuance of a prescription drug regulation.

(11) I reiterate my belief that restriction to prescription drug status of these high dosage oral preparations of vitamins A and D is essential for the protection of the public health, and that I regard these high dosage preparations as "drugs".

A. M. Schmidt

Alexander M. Schmidt, M.D.
Commissioner of Food and Drugs

Sworn and subscribed to before me this 21st day of March, 1975, at Rockville, Maryland.

Mary B. Garrett

Notary Public
MARY B. GARRETT

My Commission Expires July 1, 1978

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

VITAMIN A AND VITAMIN D

Proposed Statement of Policy

Large doses of vitamin A and/or vitamin D ingested over long periods of time can cause adverse effects, some of which are serious. Vitamins A and D are fat-soluble and excess quantities accumulate in fatty tissue. The acute and chronic toxicity of these vitamins is documented extensively in the medical literature. Vitamin A is available over the counter in dosage levels up to 10 times the recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council (NAS–NRC), and vitamin D is available up to 60 times the RDA. The availability without prescription of these vitamins in high dosage levels contributes significantly to their misuse and the occurrence of serious adverse effects.

In view of the toxicity of excessive quantities of these vitamins, it is of concern to the Food and Drug Administration and medical authorities that there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders. In its "Newsletter" of June 1, 1972 (Vol. 23, No. 9), the American Academy of Pediatrics (AAP) comments on the critical dangers of use of high doses of vitamin A that have been recommended in the lay press, on radio, and on television. For example, the layman is being advised that he would profit from taking 25,000 international units (IU) of vitamin A with [illegible] IU of vitamin D, or twice these amounts, daily.

The AAP Committees on [illegible] on Nutrition published a joint [illegible] statement entitled "The Use and Abuse of Vitamin A" in the journal "Pediatrics," Volume 48, Number 4, October 1971, warning physicians regarding vitamin A toxicity. This article states: "Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through easy availability of high potency vitamin preparations without prescription and by the overzealous parents who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods." The AAP Committee on Drugs specifically has urged the Food and Drug Administration to limit the potency of vitamin A preparations available over the counter.

There exists considerable information in the literature regarding these vitamins and their toxicity. A listing of a number of pertinent articles, many of them recent, regarding these vitamins has been placed on file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, Md. 20852 for public view.

The highlights regarding toxicity of vitamins A and D and the rationale for limiting over-the-counter availability of these vitamins are as follows:

VITAMIN A

Adverse effects which result from excess intake of vitamin A include anorexia, growth retardation in children, drying and cracking of the skin, hepatosplenomegaly, increase intracranial pressure, alopecia, migratory arthralgia, bone pain,

hypomenorrhea, irritability, and headache. Doses of 50,000 IU in adults and 20,000 IU in infants on a daily basis over long periods are known to produce toxicity. At present vitamin A is available over the counter in dosage levels as high as 50,000 IU per dosage unit. In recent years, some physicians and laymen have used large doses of vitamin A in the treatment of acne, although such therapy has not been shown to be safe and effective. Vitamin A in excessive dosages is used over long periods of time for this indication. Adverse effects, particularly increased intracranial pressure which may mimic a brain tumor, have been observed in children and young adults who are receiving vitamin A therapy for the treatment of acne. Reports of such effects have been published in the medical literature.

The position of the AAP on the matter is clear, as cited above.

In the United States, the Food and Nutrition Board, NAS/NRC, is the recognized authority for determining vitamin and other nutritional requirements for the human. The recommended daily dietary allowances (RDA) of the Food and Nutrition Board for vitamin A are 1,500 IU for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for older children and adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

Based on the above considerations, it is the opinion of the Food and Drug Administration and medical experts that preparations containing vitamin A in excess of 10,000 IU per dosage unit shall be dispensed only by prescription and that for any vitamin A preparation intended for distribution as a dietary supplement or as an over-the-counter drug, the recommended daily dosage shall not exceed 10,000 IU vitamin A.

VITAMIN D

There are marked differences in tolerances to Vitamin D in humans when quantities in excess of normal requirements are ingested over prolonged periods. There are significant numbers of individuals who are hyperreactive to excess vitamin D. Generally, the margin of safety between nutritional requirements and toxic levels is small for vitamin D. The margin is particularly small in those individuals who are hyperreactive.

In infants, children and adults, excessive ingestion of vitamin D results in hypervitaminosis D characterized by anorexia, nausea, weakness, weight loss, polyuria, constipation, vague aches, stiffness, generalized vascular, soft tissue and premature epiphyseal calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure and death.

Daily ingestion by infants of doses between 1,000 and 2,000 IU has produced hypervitaminosis D, usually manifested as the infantile hypercalcemia syndrome. There is good evidence suggesting that the supravalvular aortic stenosis syndrome with hypercalcemia in infants and children may result from excess intakes of vitamin D by the infant and/or by the mother during pregnancy. This latter syndrome may have a tragic outcome with severe aortic stenosis, mental and physical retardation, elfin facies, renal failure and death.

The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin D for all age groups for which the vitamin is required is 400 IU. Although a daily intake of 400 IU of vitamin D is sufficient to prevent vitamin D deficiencies, preparations are available over the counter in dosage levels up to 25,000 IU per dosage unit. Excessive dosages of vitamin D have also been promoted in the lay press as noted above.

Based on the toxicity of vitamin D, the possibility of severe irreversible adverse effects in some instances, and the narrow margin of safety, it is the consensus of medical experts and the Food and Drug Administration that preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed only by prescription and that the recommended daily dosage of any vitamin D preparation marketed as a special dietary food or as an over-the-counter drug shall not exceed 400 IU.

Therefore, because of the toxicity of vitamins A and D, their continued promotion in high doses to the lay person, and the continuing reports of adverse effects attributable to excessive intake of these vitamins, the FDA concludes it is in the interest of consumer safety to take the action herein described.

All vitamins are included among the over-the-counter drugs to be reviewed by an OTC Drug Advisory Review Panel, under the procedures established in the FEDERAL REGISTER on May 11, 1972 (37 F.R. 9464). Safety and effectiveness and more general questions related to adequate labeling of vitamin preparations marketed as OTC drugs will be considered by that panel, as well as the differences between foods for special dietary use, OTC drugs, and prescription drugs as they relate to vitamins. The Food and Drug Administration will publish, in the near future, new regulations governing dietary supplements of vitamins and minerals. Until such time as the OTC Drug Advisory Review Panel has completed its review and the new regulations for dietary supplements of vitamins and minerals are in effect, the Food and Drug Administration will not object to the inclusion in vitamin products marketed as foods for special dietary use or as OTC drugs of vitamin D at levels not exceeding 400 IU per dosage unit or 10,000 IU of vitamin A per dosage unit and with the recommended daily dosage not exceeding 400 IU of vitamin D or 10,000 IU of vitamin A.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502 (a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352 (a), (f), and (j), 353 (b), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes to amend Part 3 by adding the following new sections:

§ 3.— Vitamin A preparations for oral use as drugs.

(a) Vitamin A is clearly known to be an essential nutrient for humans. Large doses of vitamin A can cause adverse effects, some of which are serious. The toxicity of vitamin A is well documented in the medical literature. The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin A are: 1,500 international units (IU) for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

(b) In view of the toxicity from the use of large doses of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(3) The recommended daily dosage of vitamin A does not exceed 10,000 IU.

(c) Vitamin A preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER).

§ 3.— Vitamin D preparations for oral use as drugs.

(a) The importance of vitamin D in human nutrition is established. It is also widely recognized that vitamin D, when ingested daily in excessive amounts, is toxic. The recommended daily dietary allowance of vitamin D established by the Food and Nutrition Board, National Academy of Sciences-National Research Council for the prevention of vitamin D deficiency for all age and physiological groups for which the vitamin is required is 400 IU from all sources.

(b) In view of the known toxicity and seriousness of the adverse effects that may be caused by excessive consumption of vitamin D, the Food and Drug Administration finds that in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appro-

priate warnings regarding vitamin D toxicity.

(3) The recommended daily dosage of vitamin D does not exceed 400 IU.

(c) Vitamin D preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER).

Interested persons may, within 60 days after publication thereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding these proposals. Comments may be accompanied by a memorandum or brief in support thereof. Comments received will be available for public inspection at the above office during regular business hours, Monday through Friday.

Dated: November 28, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.72-21379 Filed 12-13-72;8:45 am]

333a

PROPOSED RULE MAKING

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

VITAMIN A AND VITAMIN D

Proposed Statement of Policy; Correction

The Commissioner of Food and Drugs issued a proposed statement of policy on the use of vitamin A and vitamin D which was published in the FEDERAL REGISTER of Thursday, December 14, 1972 (37 FR 26618). The provisions of the proposed new sections should be corrected as follows:

1. The proposed § 3.—— *Vitamin A preparations for oral use as drugs* is amended by deleting paragraph (b)(3), redesignating paragraph (c) as paragraph (d), and adding a new paragraph (c) to read as set forth below.

§ 3.—— Vitamin A preparations for oral use as drugs.

* * * * * * *

(b) * * *

(3) [Deleted]

(c) Preparations containing 10,000 or less I.U. of vitamin A per dosage unit will be regarded as misbranded if their recommended daily dosage exceeds 10,000 I.U.

* * * * * * *

2. The proposed § 3.—— *Vitamin D preparations for oral use as drugs* is amended by deleting paragraph (b)(3), redesignating paragraph (c) as paragraph (d), and adding a new paragraph (c) to read as set forth below.

§ 3.—— Vitamin D preparations for oral use as drugs.

* * * * * * *

(b) * * *

(3) [Deleted]

(c) Preparations containing 400 or less I.U. of vitamin D per dosage unit will be regarded as misbranded if their recommended daily dosage exceeds 400 I.U.

* * * * * * *

Dated: December 26, 1972.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.73-132 Filed 1-3-73;8:45 am]

Approximately 2,500 comments and 1,000 signatures on petitions were received in response to the proposal. Comments were received from a wide segment of the public, including individual consumers, physicians, nurses, pharmacists, dietitians, home economists, nutritionists, nine pharmaceutical manufacturers, a number of vitamin preparation distributors, and health food store operators. Comments from the medical profession were presented by the American Academy of Pediatrics and the American Medical Association. Organized consumer groups that responded were the National Health Federation, Oregon Student Public Interest Research Group, Committee Against Health Fraud, Inc., Committee for the Cessation of "Fortification" of Food Products with Calciferol Hormones, Virginia Citizens Consumer Council, Inc., Consumers Cooperative of Berkeley, Inc. Comments were also submitted by the Wisconsin Alumni Research Foundation, The Ann Arbor Dietetic Association, the American Dietetic Association, and five trade associations: The Pharmaceutical Manufacturers Association, East Coast Health Food Corporation, the National Food, Drug and Cosmetic Association of Manufacturers and Distributors, Inc., the National Nutritional Foods Association and the National Association of Pharmaceutical Manufacturers.

General Comments

The proposal was controversial and generated widely ranging comments regarding broad issues raised by the use of vitamins in foods and drugs. Many of these comments are not appropriate for consideration of the more limited issues raised in the proposed regulation regarding vitamin A and vitamin D. With respect to the broad issues of vitamin and mineral use the Commissioner notes that several regulations including comprehensive discussion of these issues have been published in the FEDERAL REGISTERS of January 19 and March 14, 1973 (38 FR 2124, 6950) and elsewhere in this issue of the FEDERAL REGISTER.

The majority of responses from individual consumers were opposed to the proposal. In reviewing such comments, the Commissioner is concerned that the public is not fully aware of the provisions and medical basis of the proposal. For example, the tenor of many comments was that vitamin A and vitamin D would be available only on prescription. Form letters and several petitions, which were submitted with a number of signatures, contained key statements, presumably the basis on which the signatures were obtained, that bear very little, if any, resemblance to the actual provisions of the proposal. It is clear that the majority of individual consumers responding had been improperly or inadequately informed.

The comments fall into three general categories:

(1) Those who agree that the action proposed by the Food and Drug Administration is necessary and that the prescription levels proposed for vitamin A and vitamin D are suitable. Those who agreed included the American Academy of Pediatrics, the American Medical Association, the American Dietetic Association, five consumer groups, a number of physicians, dietitians, nutritionists, home economists and other professionals in the scientific and health care community, and a few individual consumers.

(2) Those who agree that such vitamins can be toxic, but only at levels higher than those levels proposed by the Food and Drug Administration. The majority of the drug manufacturers and trade associations, and some consumers, made responses that were in this category.

(3) Those who disagree with the proposal entirely, stating that such vitamins are foods and that individuals should have the right to ingest any amount desired. The comments from most individual consumers, operators of health food establishments and a consumer group, were in this category.

Specific Comments

1. A number of comments contended that "natural" vitamins (including vitamin A and vitamin D) and minerals are foods rather than drugs and should not be treated as drugs. Some viewed "natural" vitamins as safe whereas synthesized vitamins may be (or are) toxic.

The question regarding whether a vitamin is a food or drug generated considerable discussion. The tentative and final orders promulgating §§ 80.1, [illegible], and 125.3 (21 CFR 80.1, 125.1 and [illegible]), published in the January 19, [illegible] FEDERAL REGISTER (38 FR 2143, 2144) [illegible] elsewhere in this issue of the FEDERAL REGISTER discuss this matter in detail. The Commissioner concludes, on the basis of all the available evidence, that vitamins between the upper and lower limits as specified in § 80.1 are adequate for all known nutritional needs for normal individuals and that nutrients at these levels are dietary supplements which are foods for special dietary use. No evidence was submitted in the comments to establish a food or nutritional use of vitamin A or vitamin D at higher levels, except for a limited number of persons with poor vitamin D absorption who need up to 1000 IU of this vitamin for nutritional purposes under medical supervision. With that one exception, which is recognized in the revised regulation, intake of vitamins at levels exceeding the upper limits as specified in § 80.1 are therefore appropriate only for therapeutic purposes and thus are properly classed as drugs.

This position is entirely consistent with the Food and Drug Administration's long-standing interpretation and application of the act. See, e.g., Mordel v. United States, 335 U.S. 345 (1948), in which the Supreme Court upheld the conviction of an individual for marketing "health food products" consisting of "various vitamins, minerals, and herbs" on the ground that they were misbranded drugs. See also United States v. 3 Cartons * * * "No. 26 Formula GM etc.," 132 F. Supp. 569 (S.D. Calif. 1952).

Alleged differences in vitamins based on their source is also discussed in the

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

Status of Vitamin A and Vitamin D

In the FEDERAL REGISTER of December 14, 1972 (37 FR 26618) the Commissioner of Food and Drugs proposed that preparations containing vitamin A in excess of 10,000 international units (IU) per dosage unit and preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed on prescription. A correction, which did not alter the intent of the proposal, was published in the FEDERAL REGISTER of January 4, 1973 (38 FR 799). Sixty days were allowed for comment.

tentative and final orders promulgating §§ 80.1 and 125.1–125.3. There is no scientific evidence to suggest that there is a difference in the metabolic actions or toxic effects of synthetically produced vitamins as compared with those from natural sources.

2. Several manufacturers and trade associations objected to the proposal on the ground that the proper classification of OTC drug levels of vitamins would be made in the near future by the appropriate OTC drug advisory review panel and that levels established now by the Food and Drug Administration would only be on interim measure. These comments expressed the opinion that deferring action on this proposal would not result in any signficant hazard to the public health.

In the preamble of the proposal the Commissioner stated his reasons for separating vitamin A and vitamin D from the other vitamins at this time and establishing levels above which these vitamins are limited to prescription distribution. The continuing information available to the Commissioner regarding the toxicity of vitamin A and vitamin D and the continuing reports of promotion of large amounts of these vitamins for a variety of purposes makes this action necessary at this time in the public interest.

3. A number of comments from individual consumers and those representing the vitamin industry agreed that vitamin A and vitamin D are toxic in amounts in excess of known requirements, but stated that such levels are much higher than the limitations proposed. Some comments offered a level of 25,000 IU of Vitamin A and 1,000 IU of Vitamin D as providing a sufficient safety margin for known toxicity. Other comments contended that the proposed levels were suitable for children, but higher levels would be more appropriate for adults. A number of comments felt the proposed levels were arbitrary and without scientific merit or support. Several of the comments had made a review and provided their own analysis of the bibliography prepared by the Food and Drug Administration at the time the proposal was published in the FEDERAL REGISTER. Generally, these comments stated that toxicity below 50,000 IU daily for vitamin A was rare and that vitamin D toxicity reports would not support the vitamin D level proposed.

Several other comments recommended lower levels than those proposed. A comment from a physician at a university School of Medicine, Department of Biochemistry, supported the proposal, but stated that 5,000 IU for vitamin A would be a more judicious level. Another comment from the Department of Chemical Pathology, the United Liverpool Hospitals, Liverpool, England, included a reference to a paper written by the respondent regarding self-medication with multivitamin preparations and recommended that 100 IU of vitamin D per dosage unit be the limit for non-prescription marketing.

The Commissioner has carefully reviewed the comments and analysis regarding the medical/scientific justification for establishing the proposed vitamin A and vitamin D limits and finds that such comments do not sufficiently support a revision of the proposed limits. No evidence refuted the toxicity findings on which the proposal was based, and further reports of toxicity continue to accumulate. Based on consultation with the most knowledgeable experts available, the Commissioner finds that the scientific consensus is that the proposed limits are appropriate at this time.

The Commissioner of Food and Drugs will soon publish in the FEDERAL REGISTER a request for submission of all data and information relevant to the safety and effectiveness of vitamins and minerals for OTC drug use, pursuant to the procedures established in 21 CFR 130.301, published in the FEDERAL REGISTER on May 11, 1972 (37 FR 9464). The members of the OTC drug review panel for vitamin-mineral drugs are presently being selected. This panel will have full authority to review and re-evaluate the proper dividing line between OTC and prescription levels of vitamin A and vitamin D, and to recommend to the Commissioner changes in the regulations promulgated by this order, in its report. Thus, the levels of vitamin A and vitamin D for prescription use in this regulation are established on an interim basis only. These regulations will be revoked upon promulgation of a final OTC drug monograph for vitamin-mineral drugs incorporating final prescription levels for these two vitamins.

4. A number of comments, particularly those from individual consumers, state that it is not logical to require a prescription for dosage levels of vitamins that may be lower than the vitamin content of an average serving of certain foods. A few comments expressed concern that normal diets with or without appropriate vitamin supplementation may lead to toxic conditions.

The Commissioner recognizes that many common foods contain a variety of vitamins and minerals in widely ranging amounts, and that some common foods contain vitamin A in excess of 10,000 IU per serving. It is also recognized, however, that these foods particularly rich in vitamin A are rarely consumed daily in sufficient quantity over the long periods of time required to lead to toxic manifestations. The concern of the Food and Drug Administration is the availability of vitamin A and vitamin D in large dosage units in medicinal forms, i.e. capsules and tablets, particularly in view of the multiplicity of other sources of this vitamin in the daily diet. The convenience of ingestion in this form on a routine basis encourages excessive intake of these vitamins far beyond the average amounts ingested in normal diets of conventional food over extended periods of time. Adequate amounts of vitamin A and vitamin D will continue to be available as dietary supplements and are not being removed from the market place. The margins of safety provided in the levels established by this proposal were developed to take into account the wide ranges of vitamin content in foods and the dosage levels of vitamin A and vitamin D preparations that are usually implicated in toxic conditions.

5. Comment was received that consumers would be able to ingest as many dosage units as they desired and therefore the proposed limits would have no effect. The Commissioner cannot agree with this concept. Today's consumers are increasingly knowledgeable and are concerned about the health and safety of themselves and their family. The Commissioner believes that most consumers will carefully consider the advisability of taking dosage units in excess of suitable recommended daily dosages. Conscientious consumers will have a basis upon which to make a judgment as to their intake of these vitamins. The fact that a small number of consumers will abuse their health by excessive intakes of drugs, regardless of regulatory and other approaches to curtail such abuse, is no reason to forego a reasonable regulation that will afford appropriate public health protection for the vast majority of the public.

6. The Committee on Nutrition, American Academy of Pediatrics, and several other respondents commented on the special needs for vitamin D in foods for special dietary use in specific medical conditions. Foods designed to provide sound nutrition to individuals with poor vitamin D absorption require higher than normal levels of vitamin D. Such individuals may require dietary intakes up to 1000 IU as part of their overall dietary management.

The Commissioner recognizes that foods represented solely for use under medical supervision to meet nutritional requirements in specific medical conditions have a place in medical care of a select group of individuals who have diagnosed conditions that will benefit from the use of complete foods containing up to 1000 IU of vitamin D. The marketing of such foods is permitted in compliance with § 125.1(h) being published elsewhere in this issue of the FEDERAL REGISTER. The regulation for vitamin D has been revised to allow this limited use of a higher amount of vitamin D without a prescription.

7. Comments received from the Council on Foods and Nutrition, American Medical Association, endorse the proposal and include reference to the possible relationship between excess vitamin D and hypercholesterolemia, in addition to the classic form of vitamin D toxicity. The Council also commented that the proposal fails to mention that there is no recommended dietary allowance for vitamin D for adults, since their needs are considered to be met by ordinary mixed diets and exposure to sunlight. The Council, along with other respondents, raised a question regarding a controlled "overage" to assure compliance with label declarations of the amounts present.

The Food and Drug Administration recognizes that there is no recommended dietary allowance for vitamin D in adults except during pregnancy and lactation and therefore considers vitamin D as an

optional component of dietary supplements of vitamins and minerals for adults and older children (21 CFR 80.1). The Commissioner notes that within good manufacturing practices reasonable overages are permissible in formulating drugs and these are recognized in the specification ranges used in determining whether or not a product meets its labeled potency.

8. In response to the proposal, the Wisconsin Alumni Research Foundation resubmitted comments directed to a proposal regarding vitamin D published in the FEDERAL REGISTER of August 28, 1965 (30 FR 11140). The previous proposal was more restrictive than the present one and contained several provisions not currently being considered. Of significance in this comment was concern by the Wisconsin Alumni Research Foundation that the requirements as proposed in 1965 would have the effect of decreasing the vitamin D intake by the general public to a level below their nutritional needs.

The Commissioner concludes that such a situation is clearly not possible as a result of the current proposal, which is directed only at the use of vitamin D as a drug. As a result of the vitamin D content of milk and other foods, and the availability of vitamin D in dietary supplements, the national food supply provides ample vitamin D.

9. Several manufacturers commented that the effective date of any final order with respect to vitamin A and vitamin D should be the same uniform effective date established for recent food labeling revisions. Such an effective date would permit interstate shipments of existing high potency products through December 31, 1974. Several comments also requested that those vitamin A and vitamin D preparations already in commercial channels be allowed continued marketing until existing supplies are exhausted.

Because of the known toxicity and continuing reports of toxic conditions resulting from large dosages over a period of time, the Commissioner concludes that protracted continuation of manufacture [illegible] marketing [illegible]parations that do not meet the r[illegible]ents of this order is not justified. [illegible]ver, a reasonable period of time [illegible] for orderly reformulation and relabeling, where necessary, is in the public interest to assure continued availability of vitamin A and vitamin D preparations. Therefore, this order shall become effective for products labeled beginning October 1, 1973. No recall of existing stocks is deemed necessary.

10. One comment from a manufacturer stated that the proposal conflicts with the limits for vitamin A established by the food labeling regulations published in the January 19, 1973 FEDERAL REGISTER (38 FR 2124). The Commissioner finds no conflict between this drug regulation and the food regulations. Those vitamin A preparations within the ranges specified in § 80.1 are considered foods and must be labeled as dietary supplements. Those preparations containing vitamin A in excess of the upper limit of these ranges, but less than the proposed prescription drug level, are OTC drugs. Those preparations containing in excess of 10,000 IU of vitamin A per dosage unit are prescription drugs.

11. Several comments requested that a public hearing be held to consider the issues and objections. A hearing on these matters is not mandatory under section 701(a) of the act. The Commissioner concludes that a hearing is inappropriate at this time and that any further delay in promulgation of these regulations is not in the public interest. A hearing on this issue will be available before both the advisory drug panel and the Commissioner under the OTC drug review procedures.

Having considered the comments received, the Commissioner concludes that the proposed regulations are in the public interest and should be adopted as set forth below.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), Part 3 is amended by adding thereto the following new sections:

§ 3.94 Vitamin A preparations for oral use as drugs.

(a) Vitamin A is an essental nutrient for humans. It is widely recognized that large amounts of vitamin A can cause adverse effects, some of which are serious. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin A is 1500 International Units, (IU) for infants, 2500 IU for children under 4 years of age, 5000 IU for adults and children 4 or more years of age, and 8000 IU for pregnant or lactating women.

(b) In view of the toxicity of excessive consumption of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(c) Preparations containing 10,000 or less IU of vitamin A per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 10,000 IU.

§ 3.95 Vitamin D preparations for oral use as drugs.

(a) Vitamin D is an essential nutrient for humans. It is widely recognized that vitamin D, when ingested daily in large amounts, is toxic. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin D is 400 International Units (IU).

(b) In view of the toxicity of the excessive consumption of vitamin D, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin D toxicity.

(c) Preparations containing 400 or less IU of vitamin D per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 400 IU.

(d) Foods which are represented for use solely under medical supervision to meet nutritional requirements of persons with poor vitamin D absorption may contain vitamin D not in excess of 1000 IU per dosage unit or recommended daily intake.

Effective date. This order shall become effective on October 1, 1973 for products labeled on or after that date.

(Secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a))

Dated: July 25, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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AMA DRUG EVALUATIONS

SECOND EDITION

Prepared by the
AMA DEPARTMENT OF DRUGS

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PREFACE

The second edition of *AMA Drug Evaluations (AMA-DE)* was compiled by the AMA Department of Drugs under the direction of the former AMA Council on Drugs. It provides reliable and current scientific information for those who prescribe, dispense, and administer drugs.

Readers familiar with the first edition will detect significant new features and changes in format. Among these are (1) a smaller, more convenient size, (2) a hard cover, (3) indexing by trade name as well as generic name, (4) inclusion of structural formulas, (5) use of conventional prose instead of telegraphic style in the individual evaluations, and (6) expanded coverage of information on drug interactions. The New Drugs Section and the Indications Index have been eliminated.

AMA-DE describes uses, routes of administration, or dosages that may not be found in the "package insert." FDA-approved labeling limits the use of drugs for purposes of marketing and advertising but does not rigidly constrain a physician's use of the drug for individual patients. Accordingly, *AMA-DE* describes all scientific, recognized uses of drugs irrespective of their status in approved labeling in the "package insert."

In the 2½ years since the first edition, many drug products have been removed from the market by the FDA as the result of the Drug Efficacy Study by the National Academy of Sciences-National Research Council. Every effort has been made to delete these products from the text. Because of the time lag between preparation of final copy and publication, however, some drugs are described that are no longer available.

The American Medical Association hopes that the second edition of *AMA-DE* will be a valuable and useful service to the medical profession and to others working in the field of medical care.

ERNEST B. HOWARD, M.D.
Executive Vice President

Chapter 14

VITAMINS AND SOURCES OF VITAMINS

The vitamins in purified form are available individually or in various combinations in a wide variety of pharmaceutical preparations: some are for prophylactic use as dietary supplements and others are suitable only for use as therapeutic agents. Both types often are used indiscriminately and inappropriately. Under usual circumstances, healthy persons consuming an adequate balanced diet can expect no benefit from additional vitamins. Moreover, the danger of toxic effects from excessive amounts of vitamins A or D, particularly in infants and children, must be kept in mind.

The AMA Council on Foods and Nutrition states that an adequate diet will supply all the nutrients needed by the normal individual but that both dietary adequacy and nutritional requirements are influenced by many factors. Thus, appropriately formulated vitamin supplements may be indicated to meet temporarily increased demands (eg, in pregnancy and lactation) and to assure proper growth and development during infancy and childhood. Supplementation also may be indicated to compensate for decreased intake or absorption during illnesses or when the diet is inadequate for any reason. It frequently is difficult for the physician to ascertain dietary adequacy, but whenever possible, poor dietary habits due to such factors as ignorance, poverty, food fads, poor dentition, emotional upset, or temporarily changed living pattern should be corrected, thus eliminating further need for supplementation.

Recent surveys reveal that vitamin nutriture is less satisfactory in larger segments of the population than previously believed. For example, levels of some nutrients (eg, vitamin A, ascorbic acid) may be suboptimal or inadequate in the diets of certain low-income families and ethnic groups. These people might benefit from vitamin supplementation at the same time that their diet is being improved. Many disadvantaged preschool children showed evidences of malnutrition, including abnormalities of hair and skin, cheilosis, goiter, mild growth retardation, and decreased stores of vitamin A, iron, folic acid, and thiamine.

Of the fat-soluble vitamins, vitamins A, D, and E are discussed in this chapter. The therapeutic and prophylactic uses of vitamin K in hypoprothrombinemic conditions (eg, hemorrhagic disease of the newborn, overdosage of anticoagulants) are discussed in Chapter 11, Hemostatics.

The water-soluble vitamins to be discussed are ascorbic acid (vitamin C) and the B-complex vitamins, which include niacin (nicotinic acid), pantothenic acid, pyridoxine, riboflavin, and thiamine. Folic acid and cyanocobalamin (vitamin B_{12}), which also are considered members of the B-complex group, will be discussed in this chapter only in relation to their inclusion in supplemental multivitamin preparations. (See also Chapter 8, Agents Used to Treat Deficiency Anemias.)

The Recommended Dietary Allowances (RDA) for individual vitamins established by the Food and Nutrition Board of the National Research Council provide authoritative information to assist the physician in evaluating the formulas of multivitamin preparations. (See also the section on Mixtures.) These allowances, shown in Table 1, represent amounts that will maintain good nutrition in practically all healthy persons, and are usually considerably greater than the Minimum Daily Requirements (MDR) established by the Food and Drug Administration for labeling purposes. The allowances for calories and protein also are shown in Table 1, since the requirements for many of the B vitamins are related to caloric intake. (In nutrition, the calorie used is the

TABLE 1.—RECOMMENDED DAILY DIETARY ALLOWANCES[1]

	Ages (years)	Weight (kg)	Height (cm)	Kilocalorie (kcal)	Protein (g)	Fat-Soluble Vitamins: Vitamin A Activity (IU)	Vitamin D (IU)	Vitamin E Activity (IU)
Infants	0 to ⅙	4	55	kg x 120	kg x 2.2	1,500	400	5
	⅙ to ½	7	63	kg x 110	kg x 2.0	1,500	400	5
	½ to 1	9	72	kg x 100	kg x 1.8	1,500	400	5
Children	1 to 2	12	81	1,100	25	2,000	400	10
	2 to 3	14	91	1,250	25	2,000	400	10
	3 to 4	16	100	1,400	30	2,500	400	10
	4 to 6	19	110	1,600	30	2,500	400	10
	6 to 8	23	121	2,000	35	3,500	400	15
	8 to 10	28	131	2,200	40	3,500	400	15
Males	10 to 12	35	140	2,500	45	4,500	400	20
	12 to 14	43	151	2,700	50	5,000	400	20
	14 to 18	59	170	3,000	60	5,000	400	25
	18 to 22	67	175	2,800	60	5,000	400	30
	22 to 35	70	175	2,800	65	5,000	—	30
	35 to 55	70	173	2,600	65	5,000	—	30
	55 to 75+	70	171	2,400	65	5,000	—	30
Females	10 to 12	35	142	2,250	50	4,500	400	20
	12 to 14	44	154	2,300	50	5,000	400	20
	14 to 16	52	157	2,400	55	5,000	400	25
	16 to 18	54	160	2,300	55	5,000	400	25
	18 to 22	58	163	2,000	55	5,000	400	25
	22 to 35	58	163	2,000	55	5,000	—	25
	35 to 55	58	160	1,850	55	5,000	—	25
	55 to 75+	58	157	1,700	55	5,000	—	25
Pregnancy				+200	65	6,000	400	30
Lactation				+1,000	75	8,000	400	30

Adapted from Report of Food and Nutrition Board, National Academy of Sciences-National Research Council, 7th Revised Edition, 1968.

kilocalorie, or the amount of energy required to raise the temperature of 1 kilogram of water 1 C.)

It is often assumed that a dietary intake of less than the Recommended Dietary Allowance by itself indicates substandard nutrition or even a deficiency. There is no justification for such a belief. In the 1968 edition of its publication, *Recommended Dietary Allowances*, the Food and Nutrition Board states:

> "Food-consumption survey data cannot be used alone as a measure of nutritional adequacy. In determining nutritional status, the current and past nutrient intake must be taken into consideration, as well as an evaluation of clinical signs and symptoms, growth and development, and biochemical data on tissue and excretory levels of nutrients. Since the RDA are designed to be adequate for practically all of the population of

Water-Soluble Vitamins[a]

Ascorbic Acid (mg)	*Niacin (mg equiv)*[5]	*Riboflavin (mg)*	*Thiamine (mg)*	*Vitamin B_6 (mg)*	*Folacin*[6] *(mg)*	*Vitamin B_{12} (μg)*
35	5	0.4	0.2	0.2	0.05	1.0
35	7	0.5	0.4	0.3	0.05	1.5
35	8	0.6	0.5	0.4	0.1	2.0
40	8	0.6	0.6	0.5	0.1	2.0
40	8	0.7	0.6	0.6	0.2	2.5
40	9	0.8	0.7	0.7	0.2	3
40	11	0.9	0.8	0.9	0.2	4
40	13	1.1	1.0	1.0	0.2	4
40	15	1.2	1.1	1.2	0.3	5
40	17	1.3	1.3	1.4	0.4	5
45	18	1.4	1.4	1.6	0.4	5
55	20	1.5	1.5	1.8	0.4	5
60	18	1.6	1.4	2.0	0.4	5
60	18	1.7	1.4	2.0	0.4	5
60	17	1.7	1.3	2.0	0.4	5
60	14	1.7	1.2	2.0	0.4	6
40	15	1.3	1.1	1.4	0.4	5
45	15	1.4	1.2	1.6	0.4	5
50	16	1.4	1.2	1.8	0.4	5
50	15	1.5	1.2	2.0	0.4	5
55	13	1.5	1.0	2.0	0.4	5
55	13	1.5	1.0	2.0	0.4	5
55	13	1.5	1.0	2.0	0.4	5
55	13	1.5	1.0	2.0	0.4	6
60	15	1.8	+0.1	2.5	0.8	8
60	20	2.0	+0.5	2.5	0.5	6

[1]The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. The recommended allowances can be attained with a variety of common foods, providing other nutrients for which human requirements have been less well defined.

[2]No allowance has been established for pantothenic acid, but it is estimated that a daily intake of 5 to 10 mg is probably adequate for children and adults.

[3]Entries on lines for age range 22-35 years represent the reference man and woman at age 22. All other entries represent allowances for the midpoint of the specified age range.

[4]Factors for infants assume protein equivalent to human milk. For proteins not 100% utilized factors should be increased proportionately.

[5]Niacin equivalents include dietary sources of the vitamin itself plus 1 mg equivalent for each 60 mg of dietary tryptophan.

[6]The folacin allowances refer to dietary sources as determined by *Lactobacillus casei* assay. Pure forms of folacin may be effective in doses less than ¼ of the RDA.

the United States, they allow a margin of safety for individual variations. Individuals whose diets do not meet the RDA are not necessarily suffering from malnutrition, and diets should not be judged 'poor' on an arbitrary figure based on a comparison with the RDA, which are revised about every five years in order to include new research findings."

Infants most often require supplemental ascorbic acid, vitamin D, and sometimes vitamins A and E. Breast-fed infants should receive a vitamin D supplement. Artificially fed infants should receive ascorbic acid (or orange or tomato juice) and vitamin D, starting within the first week of life, if the formula does not supply 35 mg of ascorbic acid and 400 units of vitamin D. If the formula is high in polyunsaturated fatty acids, they should receive a supplement of vitamin E daily, especially if they are premature.

Infants receiving unfortified skimmed milk formulas should be given 1,500 IU of vitamin A daily. In some situations (eg, infants and children who are not eating and not developing satisfactorily, or who have diarrhea) the physician may deem it advisable to prescribe a B-vitamin supplement.

Healthy growing children consuming an adequate diet require no vitamin supplement unless they do not drink vitamin D-fortified milk and do not have sufficient exposure to sunlight; if a supplement is required, 400 units of vitamin D should be given daily. Similarly, healthy adults require no supplementation except in pregnancy and lactation when vitamin D and possibly certain of the B vitamins may be needed. There is no scientific evidence that elderly persons consuming an adequate diet have higher requirements for vitamins than do other healthy adults.

Because of increased metabolic demands, high potency B-complex and ascorbic acid supplements are indicated in patients with prolonged fever and a large daily fluid intake. These vitamins also are indicated when demand is increased by stress (eg, severe trauma, burns). In order to assure adequate replenishment of these micronutrients when total parenteral nutrition is needed, replacement doses of all the essential water-soluble vitamins should be given daily (see Chapter 16, Replenishers and Regulators of Water, Electrolytes, and Nutrients). The fat-soluble vitamins, A, D, and E, generally are not needed unless the patient's initial nutritional status is poor or his need for total parenteral nutrition is unduly prolonged. However, patients being maintained by total parenteral nutrition (especially infants) may require vitamin K because of reduced synthesis by intestinal bacteria.

Folic acid and ascorbic acid are removed by dialysis, and patients being dialyzed become deficient unless they receive compensatory amounts of these vitamins. The requirement for other vitamins apparently is not increased by dialysis.

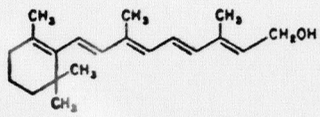
Adverse Reactions and Precautions

Therapeutic doses of niacin may cause some transient unpleasant reactions, such as flushing, tingling sensations, and a feeling of warmth; niacinamide does not cause these effects. Hepatotoxic effects have occurred in patients receiving large doses of niacin. Anaphylactic reactions have occurred after the intravenous administration of large doses of thiamine and niacin. Occasionally, B-complex vitamin preparations may cause urticaria, angioedema, pruritus, and contact dermatitis. For precautions in the use of folic acid and cyanocobalamin, see Chapter 8, Agents Used to Treat Deficiency Anemias.

Vitamin E has produced adverse effects only when doses greatly exceeded the Recommended Dietary Allowances, and the effects were reversible when the dosage was lowered.

Excessive doses of vitamins A and D produce hazardous toxic effects. See the individual evaluations on these agents.

VITAMIN A



Vitamin A is essential for normal visual functioning of the retina, normal functioning of various epithelial surfaces, and normal growth and development of bone. Eggs, dairy products, and meat (especially liver) supply preformed vitamin A. Green and yellow vegetables and fruits supply provitamins A, principally beta carotene, which the body converts to active vitamin A. Dietary fat is essential for effective absorption of carotenes, whereas protein is more important in the absorption of preformed vitamin A. Adequate liver reserves of vitamin A can prevent signs of deficiency for prolonged periods of deprivation.

Human milk supplies sufficient vitamin A unless the maternal diet is grossly inadequate. However, infants fed unfortified skimmed milk or milk-free formulas should receive a vitamin A supplement. Premature infants especially may have low liver reserves and may require an additional 500 to 1,000 IU daily to supplement dietary sources. In healthy children and adults consuming an adequate diet, vitamin A supplementation is unnecessary and is potentially hazardous if large doses are given.

Supplementary administration is useful in diseases that interfere with the absorption of vitamin A (eg, tropical sprue, cystic fibrosis, infantile or adult celiac disease, biliary obstruction, total gastrectomy). Severe hypovitaminosis A is rare in the United States, although it is still a serious and sometimes fatal disease in many parts of the world. An early sign is night blindness (nyctalopia). More severe

deficiencies, which occur chiefly in children, result in xerophthalmia which, if untreated, progresses to corneal ulceration, perforation, keratomalacia, and blindness.

Epithelial changes in vitamin A deficiency impair local defenses against infection, and deaths from severe deficiency are usually due to bronchopneumonia. These observations led to the designation of vitamin A as the anti-infective vitamin; however, vitamin A in excess of normal requirements is of no value in the prevention or treatment of infections, including common respiratory infections. Neither does evidence warrant the use of vitamin A in the prevention of renal calculi or the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, or cutaneous ulcerative conditions. Oral administration of vitamin A in large doses has been used as adjunctive therapy in acne, but proof of efficacy is lacking and the treatment is not generally accepted. The topical use of cod liver oil or other preparations containing vitamin A in the treatment of wounds and other local conditions has not been supported by controlled studies.

Vitamin A is toxic in excessive doses, and clinical cases of hypervitaminosis A appear to be increasing. Preparations containing 25,000 IU or more are available without prescription even though such dosages generally should be restricted to patients with severe vitamin A deficiency. Daily doses as low as 18,500 IU in a water-dispersed preparation with vitamin D for one to three months have been reported to produce signs of overdosage in infants 3 to 6 months of age. Manifestations of hypervitaminosis A include anorexia, weight loss, pruritus, cracking and bleeding of lips, fatigue, abdominal discomfort, ostealgia or arthralgia, pseudotumor cerebri, insomnia, alopecia, brittle nails, menstrual irregularities, hyperostoses, and premature closure of the epiphyses. Most of these disorders improve within a week after withdrawal of the drug. Excessive intake of carotene does not cause signs or symptoms of hypervitaminosis A because its conversion to vitamin A is slow and incomplete. A high carotene intake may cause yellowish discoloration of the skin that resembles jaundice, except that it does not involve the sclera; patients with hypothyroidism are especially susceptible to this effect.

USUAL DOSAGE.—
Oral: Infants fed unfortified skimmed milk or other formulas, 1,500 IU. *Adults and children*, for supplementation, dosage should be based on Recommended Dietary Allowance after evaluation of patient's dietary supply. For mild to moderate clinical signs of vitamin A deficiency without corneal involvement, 25,000 to 50,000 IU daily, preferably as an aqueous dispersion, until clinical improvement has occurred; the same dosage should be used after intramuscular therapy in patients with corneal involvement. Daily doses of 50,000 IU or more have been used to treat hypovitaminosis A and other conditions such as hyperkeratotic dermatoses, but such large doses should be restricted to relatively short-term therapy because of the danger of hypervitaminosis A. Correction of the diet or reduction of the dose on the basis of Recommended Dietary Allowances should be substituted for therapeutic administration after response is obtained.

Intramuscular: Adults and children, in severe vitamin A deficiency, 50,000 to 100,000 IU daily for the first several days, preferably in water-dispersible form.

PREPARATIONS.—(Therapeutic; not to be used for prophylaxis.)

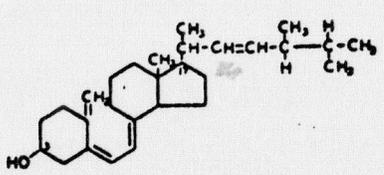
Oral: Capsules 25,000, 50,000, 75,000, and 100,000 IU; tablets 50,000 IU.

Injection: Solution 50,000 IU/ml in 5 ml containers.

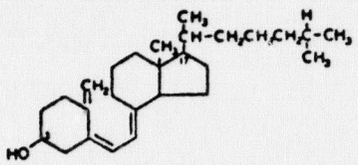
Amounts of vitamin A suitable for prophylaxis are present in some multivitamin preparations.

AVAILABLE TRADEMARKS.—Vitamin A (water-dispersible): Acon (Endo), Aquasol A (USV), Dispatabs (Person & Covey), Homagenents-Aoral (First Texas), Testavol-S (Fellows-Testagar), Vi-Dom-A (Dome), Vio-A (Rowell). Vitamin A: Alphalin (Lilly), Anatola (Parke, Davis), Haliver Oil (Parke, Davis), Super A Vitamin (Upjohn). Drug also marketed by many manufacturers under generic name.

VITAMIN D



Vitamin D_2 (ergocalciferol)



Vitamin D_3 (cholecalciferol)

The term vitamin D refers to either of two sterols, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3), that have equal antirachitic potency in man.

Vitamin D increases the absorption of calcium from the intestine, increases renal tubular reabsorption of phosphate, and aids in the mobilization of bone calcium and maintenance of calcium levels in the serum. Recent evidence concerning the action of this vitamin is of considerable potential clinical importance in the treatment of bone disease associated with chronic uremia (renal osteodystrophy) and certain other diseases that affect bone (eg, familial hypophosphatemias, Fanconi syndrome). Vitamin D itself is an inert storage form in the body and is metabolized to an active form in a series of hydroxylations at specific carbon positions. The principal metabolites identified are 25-hydroxycholecalciferol (25-HCC), which is formed in the liver, and 1,25-dihydroxycholecalciferol (1,25-DHCC), which is formed from 25-HCC in the kidney and has been shown to be the active metabolite in promoting the absorption and mobilization of calcium. The uremic kidney fails to form the active metabolite.

To some extent, both the liver and kidney hydroxylations are regulated by negative feedback mechanisms, and it has been suggested that vitamin D be considered a hormone rather than a vitamin. Nevertheless, the body must obtain vitamin D itself as the precursor of 1,25-DHCC, either from the action of ultraviolet light on sterols in the skin or from exogenous sources. Investigationally, 25-HCC is more rapidly effective in promoting calcium absorption and mobilization than is vitamin D, and 1,25-DHCC is most rapidly effective. Other hydroxy derivatives of 25-HCC have been identified which act preferentially on the intestinal absorption of calcium or the mobilization of bone calcium.

Disturbance of calcium and phosphorus metabolism in hypovitaminosis D results in rickets, infantile tetany, and osteomalacia. In addition to inadequate intake, deficiencies of vitamin D occur as a result of malabsorption (eg, celiac disease, tropical sprue, gastrointestinal resections). Most milk sold in the United States is fortified with at least 400 units of vitamin D per quart, and many other foods such as margarine and breakfast cereals contain added vitamin D. Thus, many individuals in the United States subsisting on the usual foods obtain the recommended daily allowance or more from dietary sources; however, some brands of market milk are not fortified. Irradiation of the skin by sunlight also can meet the requirement for vitamin D.

Breast-fed infants as well as infants receiving an unfortified formula require a daily supplement of vitamin D. Premature infants may have a more critical need for supplementation because they have lower calcium stores (the fetus acquires more than 85% of its calcium stores during the last trimester) and are more susceptible to rickets than are full-term infants. Supplementation is indicated in pregnancy if the diet does not supply 400 units of vitamin D. See also the Introductory Statement.

The margin of safety between prophylactic or therapeutic doses and toxic doses of vitamin D in infants and children appears to be narrower than formerly thought. Manifestations of hypervitaminosis D include hypercalcemia, ectopic calcifications (calcinosis universalis) in soft tissues (eg, heart, blood vessels, kidneys), anorexia, nausea and vomiting, diarrhea, polydipsia, polyuria, and headache. Osteoporosis, hypertension, and decreased renal function also have been observed. Complete recovery follows if the intake of vitamin D is stopped in time.

Hypervitaminosis D may occur in infants and young children receiving supplements in addition to high dietary intake or from overdosage due to parental ignorance or error. It also may be caused by large doses used in the treatment of such diseases as familial hypophosphatemia (vitamin D-resistant rickets) and renal osteodystrophy. There is some evidence of a possible relationship between vitamin D intake and idiopathic infantile hypercalcemia.

There is no satisfactory evidence to indicate that the inclusion of vitamin D in preparations for topical use is beneficial.

For information on the interrelationship of vitamin D and parathyroid hormone and the use of vitamin D and dihydrotachysterol in the treatment of the hypocalcemia of hypoparathyroidism, see Chapter 17, Blood

Calcium Regulators.

USUAL DOSAGE.—

Oral (Supplementation): Premature infants may require a supplement because of their greater susceptibility to rickets. Rarely, an infant is abnormally susceptible to rickets and may require up to 30,000 units daily to prevent deficiency. *Breast-fed infants* or those fed unfortified formulas should receive 400 units daily as a supplement. *Adults*, supplementation ordinarily is needed only during pregnancy and lactation to assure a daily intake of 400 units. *Infants and children* receiving adequate amounts of vitamin D-fortified food require no supplementation; in fact, use of a supplement can result in overdosage.

Oral (Therapeutic): Infants and children, for treatment of rickets, 1,000 to 4,000 units daily until response is obtained; for familial hypophosphatemia (vitamin D-resistant rickets), 50,000 to 200,000 units daily. *Adults*, for osteomalacia in malabsorption syndromes, 10,000 to 50,000 units; for renal osteodystrophy, 50,000 to 500,000 units daily until desired effect is achieved or toxic effects intervene.

PREPARATIONS.—(Therapeutic; not to be used for prophylaxis.)

Ergocalciferol (Vitamin D_2):

Deltalin (Lilly). *Oral:* Capsules 50,000 units.

Drisdol (Winthrop). *Oral:* Capsules 50,000 units; solution 10,000 units/ml.

ADDITIONAL TRADEMARKS.—Geltabs (Upjohn), Viosterol in Oil (Parke, Davis). Also marketed under the names Vitamin D and Calciferol.

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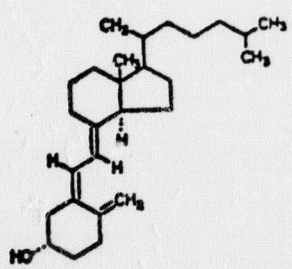
349a

Cholecalciferol

Activated 5,7-Cholestadien-3β-ol
$C_{27}H_{44}O$ 384.65



Description: White, odorless crystals. Is affected by air and by light.
Solubility: Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils.
Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, in the range of 2 μ to 12 μ, exhibits maxima only at the same wavelengths as that of a similar preparation of U. S. P. Cholecalciferol Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of U. S. P. Cholecalciferol Reference Standard, concomitantly measured, and the respective absorptivities at the wavelength of maximum absorbance at about 265 mμ do not differ by more than 3 percent.

C: To a solution of about 0.5 mg. in 5 ml. of chloroform add 0.3 ml. of acetic anhydride and 0.1 ml. of sulfuric acid, and shake vigorously: a bright red color is produced, and it rapidly changes through violet and blue to green.

D: Dissolve 50 mg. of it and 50 mg. of 3,5-dinitrobenzoyl chloride in separate 1-ml. portions of anhydrous pyridine. Mix the solutions, warm on a steam bath for 10 minutes, add 5 ml. of water, filter, and wash the precipitate thoroughly with small portions of cold water. Recrystallize the precipitate twice from acetone, and dry in a vacuum desiccator for 2 hours: the dinitrobenzoyl derivative so obtained melts between 133° and 137°.

Melting range, *Class Ib*, page 935: between 84° and 88°.

Specific rotation, page 936: not less than +105° and not more than +112°, determined in a solution in alcohol containing 50 mg. in each 10 ml. Prepare the solution without delay, using Cholecalciferol from a container opened not longer than 30 minutes, and determine the rotation within 30 minutes after the solution has been prepared.

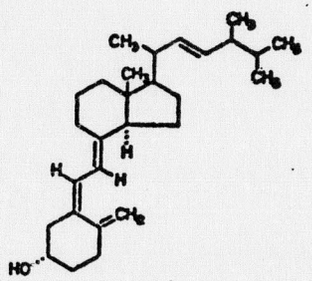
Packaging and storage—Preserve in hermetically sealed containers under nitrogen, in a cool place and protected from light.

CATEGORY: Antirachitic vitamin; also see *Decavitamin Capsules* and *Tablets*.

USUAL DOSE: In rickets—Prophylactic, 10 mcg. (400 U. S. P. Vitamin D Units) once a day.

Therapeutic, 30 mcg. (1200 Units) once a day.

In hypocalcemic tetany—1.25 to 5 mg. (50,000 to 200,000 Units) once a day.



Ergocalciferol

Irradiated Ergosta-5,7,22-trien-3β-ol
$C_{28}H_{44}O$ 396.66

Description: White, odorless crystals. Is affected by air and by light.

Solubility: Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, in the range of 2 to 12 μ, exhibits maxima only at the same wavelengths as that of a similar preparation of U. S. P. Ergocalciferol Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of U. S. P. Ergocalciferol Reference Standard, concomitantly measured, and the respective absorptivities at the wavelength of maximum absorbance at about 265 mμ do not differ by more than 3 percent.

C: To a solution of about 0.5 mg. in 5 ml. of chloroform add 0.3 ml. of acetic anhydride and 0.1 ml. of sulfuric acid, and shake vigorously: a bright red color is produced and rapidly changes through violet and blue to green.

D: Dissolve 50 mg. of it and 50 mg. of 3,5-dinitrobenzoyl chloride in separate 1-ml. portions of pyridine. Mix the solutions, warm on a steam bath for 10 minutes, add 5 ml. of water, filter, and wash the precipitate thoroughly with small portions of cold water. Recrystallize the precipitate twice from acetone, and dry in a vacuum desiccator for 2 hours: the dinitrobenzoyl derivative so obtained melts between 147° and 149°.

Melting range, *Class Ib*, page 935: between 115° and 118°.

Specific rotation, page 936: not less than +103° and not more than +106°, determined in a solution in alcohol containing 150 mg. in each 10 ml. Prepare the solution without delay, using Ergocalciferol from a container opened not longer than 30 minutes, and determine the rotation within 30 minutes after the solution has been prepared.

Ergosterol—Dissolve 10 mg. in 2 ml. of 90 percent alcohol, add a solution of 20 mg. of digitonin in 2 ml. of 90 percent alcohol, mix, and allow to stand for 18 hours: no precipitate is formed.

Reducing substances—To 10 ml. of a 1 in 100 solution in dehydrated alcohol add 0.5 ml. of a 1 in 200 solution of blue tetrazolium in dehydrated alcohol. Then add 0.5 ml. of a solution prepared by diluting 1 volume of tetramethylammonium hydroxide T.S. with dehydrated alcohol to make 10 volumes. Allow the mixture to stand for 5 minutes, then add 1 ml. of glacial acetic acid. Prepare a blank by treating 10 ml. of dehydrated alcohol in the same manner. Determine the absorbance of the solution at 525 mμ, with a suitable spectrophotometer, against the blank: the absorbance is not greater than that obtained with a solution containing 0.2 mcg. per ml. of hydroquinone in dehydrated alcohol, similarly treated.

Packaging and storage—Preserve in hermetically sealed containers under nitrogen, in a cool place and protected from light.

CATEGORY: Antirachitic vitamin; also see *Decavitamin Capsules* and *Tablets*.
USUAL DOSE: In rickets—Prophylactic, 10 mcg. (400 U. S. P. Vitamin D Units) once a day.
Therapeutic, 30 mcg. (1200 Units) once a day.
In hypocalcemic tetany—1.25 to 5 mg. (50,000 to 200,000 Units) once a day.

Ergocalciferol Capsules

Ergocalciferol Capsules usually consist of an edible vegetable oil solution of ergocalciferol, encapsulated with gelatin. Ergocalciferol Capsules contain not less than 100.0 percent of the labeled amount of $C_{28}H_{44}O$.

Oil solution content of capsules—Weigh accurately 20 Capsules in a tared weighing bottle. Soften the Capsules by exposure to 80 percent relative humidity, then carefully open as by cutting with scissors' tips, without any loss of shell material, and transfer the contents to a suitable container. Remove any oil remaining in the emptied Capsules by washing with small portions of ether, and allow the capsules to dry at room temperature until the odor of ether is no longer perceptible. Weigh the emptied capsules in the same tared bottle in which the full capsules were weighed: the difference represents the weight of the contents of the 20 Capsules.
Assay—Proceed with Ergocalciferol Capsules as directed under *Vitamin D Assay*, page 915.
Packaging and storage—Preserve in tight, light-resistant containers.
Labeling—Label the Capsules to indicate the content of ergocalciferol in mg. and in U. S. P. Vitamin D Units.
Capsules available—Capsules usually available contain the following amount of ergocalciferol: 1.25 mg. (50,000 U. S. P. Vitamin D Units).

CATEGORY and DOSE: See *Ergocalciferol*.

Ergocalciferol Solution

Ergocalciferol Solution is a solution of ergocalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. It contains, in each g., not less than 250 mcg. (10,000 U. S. P. Vitamin D Units) of $C_{28}H_{44}O$.

Description: Clear liquid having the characteristics of the solvent used in preparing the Solution.
Assay—Proceed with Ergocalciferol Solution as directed under *Vitamin D Assay*, page 915.
Packaging and storage—Preserve in tight, light-resistant containers.
Labeling—Label the Solution to indicate the concentration of ergocalciferol in mg. and in U. S. P. Vitamin D Units.

CATEGORY and DOSE: See *Ergocalciferol*.

Vitamin A

Vitamin A contains a suitable form of retinol ($C_{20}H_{30}O$; vitamin A alcohol) and possesses vitamin A activity equivalent to not less than 95.0 percent of that declared on the label. It may consist of retinol or esters of retinol formed from edible fatty acids, principally acetic and palmitic acids. It may be diluted with edible oils, or it may be incorporated in solid, edible carriers or excipients, and it may contain suitable antimicrobial agents, dispersants, and antioxidants.

Description: In liquid form, a light-yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. May be nearly odorless or may have a mild fishy odor, but has no rancid odor or taste. Is unstable to air and light.

Solubility: In liquid form, insoluble in water and in glycerin; very soluble in chloroform and in ether; soluble in absolute alcohol and in vegetable oils. In solid form, may be dispersible in water.

Identification for vitamin A—

A: To 1 ml. of a chloroform solution of it containing the equivalent of approximately 6 mcg. of retinol add 10 ml. of antimony trichloride T.S.: a transient blue color appears at once.

B: Assemble an apparatus for *Thin-layer Chromatography* (see page 796), using chromatographic silica gel as the adsorbant, and a mixture of 4 parts of cyclohexane and 1 part of ether as the solvent system. Prepare a Standard solution by dissolving the contents of 1 capsule of U. S. P. Vitamin A Reference Standard in sufficient chloroform to make 25.0 ml.

If the Vitamin A is in liquid form, dissolve a volume representing approximately 15,000 U. S. P. Units in chloroform to make 10 ml. If the Vitamin A is in solid form, weigh a quantity representing approximately 15,000 U. S. P. Units, place in a separator, add 75 ml. of water, shake vigorously for 1 minute, extract with 10 ml. of chloroform by shaking for 1 minute, and centrifuge to clarify the chloroform extract.

Apply at the starting point of the chromatogram 0.015 ml. of the Standard solution and 0.01 ml. of the solution of Vitamin A. Develop the chromatogram in the chromatographic chamber, lined with filter paper, dipping into the solvent mixture. When the solvent has ascended for a distance of 10 cm., remove the plate, and allow it to dry in air. Spray with antimony trichloride T.S.: the blue spot formed is indicative of the presence of retinol. The approximate R_f values of the predominant spots, corresponding to the different forms of retinol, are: (*alcohol* form) 0.1; (*acetate*) 0.45; and (*palmitate*) 0.7.

Absorbance ratio—The ratio of the corrected observed absorbance [A_{325}] to the absorbance A_{328} determined as directed under *Vitamin A Assay*, page 914, is not less than 0.85.

Assay—Using a suitable quantity of Vitamin A, accurately weighed, proceed as directed under *Vitamin A Assay*, page 914.
Packaging and storage—Preserve in tight containers, preferably under an atmosphere of an inert gas, protected from light.
Labeling—Label it to indicate the form in which the vitamin is present, and to indicate the presence of any antimicrobial agent, dispersant, antioxidant, or other added substance, and to indicate the vitamin A activity in terms of the equivalent amount of retinol, in mg. per g., and in U. S. P. Vitamin A Units.*

CATEGORY: Anti-xerophthalmic vitamin; also see *Decavitamin Capsules* and *Tablets*.

USUAL DOSE: Prophylactic, 1.5 mg. (5000 U. S. P. Vitamin A Units) once a day.
Therapeutic, 7.5 mg. (25,000 Units) once a day.

USUAL DOSE RANGE: Prophylactic, 1.2 to 2.4 mg. (4000 to 8000 Units) daily.
Therapeutic, 7.5 to 60 mg. (25,000 to 200,000 Units) daily.

Vitamin A Capsules

Vitamin A Capsules contain not less than 95.0 percent of the labeled amount of vitamin A.

Weight variation, page 950: meet the requirements for *Capsules*.
Other requirements—The contents of Capsules respond to the *Identification tests* and meet the requirements of the test for *Absorbance ratio* under *Vitamin A*, page 775.
Assay—Using not less than 5 Vitamin A Capsules, proceed as directed under *Vitamin A Assay*, page 914. Calculate the content of retinol ($C_{20}H_{30}O$) in mg. and in U. S. P. Vitamin A Units per Capsule.
Packaging and storage—Preserve in tight, light-resistant containers.
Labeling—Label Capsules to indicate the form in which the vitamin is present, and to indicate the vitamin A activity in terms of the equivalent amount of retinol in mg. and in U. S. P. Vitamin A Units per Capsule.
Capsules available—Capsules usually available contain the following amounts of vitamin A: 1.5, 7.5, 15, and 30 mg. (5000, 25,000, 50,000, and 100,000 U. S. P. Vitamin A Units).

CATEGORY and DOSE: See *Vitamin A*.

* NOTE—One U. S. P. Vitamin A Unit is the specific biologic activity of 0.3 mcg. of the all-*trans* isomer of retinol.

U. S. P. Reference Standards

Reference Standards are called for in many pharmacopeial assays and tests. Originally introduced for the biological assays of U. S. P. X, the use of reference standards has been extended to the point where they are now required for numerous other pharmacopeial assays as well. Some standards formerly required are still being distributed as a service to pharmacy and medicine for use as needed in unofficial assays.

On occasion, as a possible first step in pharmacopeial standardization, a reference standard or substance is provided as a standardized source of endocrine or enzyme activity in advance of the actual pharmacopeial recognition of a product representing that activity. In these cases, the articles supplied are designated as "substances" if they are heterogeneous in nature and if the prospect of their assuming pharmacopeial status is fairly remote; however, heterogeneous substances may be designated as "reference standards" if they are the counterparts of international standards.

The U. S. P. Reference Standards and U. S. P. Reference Substances are released under the authority of the U. S. P. Board of Trustees upon recommendation by the U. S. P. Reference Standards Committee, which supervises the testing and finally passes upon the suitability of each lot. The critical characteristics of the specimens selected for the standard are usually determined independently in three or more laboratories. At the request of the U. S. P. Reference Standards Committee, the Drug Standards Laboratory (*see Preface*) and the Food and Drug Administration laboratory test almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the nation, both academic and industrial, participate in the testing.

A similar program to provide international standards is maintained by the World Health Organization, an agency of the United Nations. The WHO program is concerned mainly with standards for serums, toxins, vaccines, endocrine extracts, and vitamins. As a rule, an International Standard is no longer provided once the substance responsible for its characteristic activity has been isolated, identified, and

made readily available. A limited number of such compounds are distributed under WHO sponsorship as Authentic Chemical Substances for use in assays and tests of drugs. The U. S. P. Reference Standards Committee collaborates closely with the WHO in order not only to minimize unavoidable differences in the actual units of potency but also in some cases to share in the preparation of a reference standard.

No radioactive U. S. P. Reference Standards are provided, because of the special circumstances surrounding the preparation, storage, and distribution of standardized forms of radioactive substances suitable for use in drug analyses, despite the fact that some are called for in pharmacopeial assays and tests. Reliable standards of some radioactive substances, including chromium 51, cobalt 60, gold 198, iodine 131, and phosphorus 32, are available upon order from commercial sources.

Reference Standards are not available for substances subject to the licensing provisions established for narcotics.

The following U. S. P. Reference Standards are available (the Melting Point Standards are shown in *italics*, where listed individually).

Acetanilid
Acetazolamide
Allopurinol
Amitriptyline Hydrochloride
Amobarbital
Amphotericin B
Ampicillin
Ascorbic Acid
Aspirin
Atropine Sulfate
Benzalkonium Chloride
Benzathine Penicillin G
Gamma Benzene Hexachloride
Benztropine Mesylate
Betazole Hydrochloride
Bishydroxycoumarin
Caffeine
Calcium Disodium Edetate
Calcium Pantothenate
Carbachol
Chlorambucil
Chloramphenicol
Chlordiazepoxide Hydrochloride
Chlorobenzenes
Chloroquine Phosphate
Chlorpheniramine Maleate
Chlorpromazine Hydrochloride
Chlorpropamide
Chlorthalidone
Cholecalciferol[1]
Cholestyramine Resin
Corticotropin
Cortisone Acetate
Cyanocobalamin
Cyclizine Hydrochloride
Cyclophosphamide
Cycloserine
Demecarium Bromide
Deslanoside
Desoxycorticosterone Acetate
Dexamethasone
Dexamethasone Phosphate
Dextroamphetamine Sulfate
Diaminodiphenylsulfone
Dibucaine Hydrochloride
Dichlorphenamide
Diethylstilbestrol
Diethyltoluamide
Digitalis
Digitoxin
Digoxin
Dihydrostreptomycin Sulfate
Dihydrotachysterol
Dioctyl Sodium Sulfosuccinate
Diphenhydramine Hydrochloride
Diphenylhydantoin
Disodium Edetate
Dyclonine Hydrochloride
Edrophonium Chloride
Epinephrine Bitartrate
Equilin
Ergocalciferol[2]
Ergonovine Maleate
Erythromycin
Erythromycin Ethylcarbonate
Erythromycin Gluceptate[3]
Erythromycin Lactobionate
Estradiol Valerate
Estrone
Ethacrynic Acid
Ethinyl Estradiol
Ethionamide
Ethosuximide
Ethoxzolamide
Ethynodiol Diacetate
Evans Blue
Fluorouracil
Fluoxymesterone
Folic Acid
Furosemide
Gallamine Triethiodide
Gentamicin Sulfate
Globin
Glucagon
Chorionic Gonadotropin
Griseofulvin
Guanethidine Sulfate
Hexachlorophene
Histamine Dihydrochloride
Homatropine Hydrobromide
Hydrochlorothiazide
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Sodium Phosphate
Hydrocortisone Sodium Succinate

[1] Formerly called Activated 7-Dehydrocholesterol.

[2] Formerly called Calciferol.

[3] Formerly called Erythromycin Glucoheptonate.

Hydroxychloroquine Sulfate
Hydroxyprogesterone Caproate
Hydroxystilbamidine Isethionate
Idoxuridine
Imipramine Hydrochloride
Indocyanine Green
Insulin
Iodipamide
Iodochlorhydroxyquin
Iothalamic Acid
Isoproterenol Hydrochloride
Kanamycin Sulfate
Levallorphan Tartrate
Levarterenol Bitartrate
Lincomycin Hydrochloride
Liothyronine
Lucanthone Hydrochloride
Mecamylamine Hydrochloride
Meclizine Hydrochloride
Medroxyprogesterone Acetate
Melphalan
Melting Point Standards
Meprobamate
Mercaptopurine
Mestranol
Metaraminol Bitartrate
Methamphetamine Hydrochloride
Methazolamide
Methimazole
Methotrexate Reference Substance
Methyldopa
Methyldopate Hydrochloride
Methylene Blue
Methylergonovine Maleate
Methylphenidate Hydrochloride
Metyrapone
Neomycin Sulfate
Neostigmine Bromide
Neostigmine Methylsulfate
Niacinamide
Nitrofurantoin
Norethindrone
Norethynodrel
Novobiocin
Nystatin
Ouabain
Oxytetracycline
Oxytetracycline Hydrochloride
Phenacetin
Phenacetin
Phenformin Hydrochloride
Phenobarbital
Phenolsulfonphthalein
Phenoxymethyl Penicillin
Phentolamine Mesylate[4]
Phenylephrine Hydrochloride
Physostigmine Salicylate
Phytonadione
Pilocarpine Nitrate
Posterior Pituitary
Negative Control Plastic
Polymyxin B Sulfate
Pralidoxime Chloride
Prednisolone
Prednisolone Acetate
Prednisone
Primidone
Probenecid
Procaine Hydrochloride
Prochlorperazine Maleate
Promethazine Hydrochloride
Proparacaine Hydrochloride
Propoxyphene Hydrochloride
Protamine
Pyrazinamide
Pyridostigmine Bromide
Pyridoxine Hydrochloride
Pyrimethamine
Pyrvinium Pamoate
Quinacrine Hydrochloride
Quinethazone
Quinidine Gluconate
Reserpine
Resorcinol
Riboflavin
Scopolamine Hydrobromide
Secobarbital
Sodium Ampicillin
Sodium Cephalothin
Sodium Cloxacillin
Sodium Colistimethate
Sodium Diatrizoate
Sodium Heparin[5]
Sodium Methicillin
Sodium Nafcillin
Sodium Oxacillin
Sodium Penicillin G
Sodium Sulfobromophthalein
Spironolactone
Streptomycin Sulfate
Sulfadiazine
Sulfamerazine
Sulfamethazine
Sulfanilamide
Sulfanilamide
Sulfapyridine
Sulfisoxazole
Testosterone Cypionate[6]
Testosterone Enanthate
Testosterone Propionate
Tetracaine Hydrochloride
Tetracycline Hydrochloride
Theophylline
Thiabendazole
Thiamine Hydrochloride
Thiopental
Thioridazine Hydrochloride
Thiotepa
Tolazamide
Tolbutamide
Tolnaftate
Triamcinolone
Triamcinolone Acetonide
Triamterene
Trihexyphenidyl Hydrochloride

[4] Formerly called Phentolamine Methanesulfonate.

[5] Formerly called Heparin Sodium.

[6] Formerly called Testosterone Cyclopentylpropionate.

Trimethaphan Camsylate
Tripelennamine Citrate
Tripelennamine Hydrochloride
Tropicamide
Tubocurarine Chloride
Vancomycin Hydrochloride
Vanillin
Vanillin
Vinblastine Sulfate
Vincristine Sulfate
Viomycin Sulfate
Vitamin A
Vitamin D Capsules
Vitamin D Oil
Warfarin
Zinc Bacitracin

Reference Standards and Reference Substances are available on a self-sustaining basis through orders addressed to: U. S. P. Reference Standards, 4630 Montgomery Ave., Bethesda, Md. 20014.

Vitamin A Assay

The following procedure is provided for the determination of vitamin A as an ingredient of Pharmacopeial preparations. It conforms to that which was adopted in 1956 for international use by the International Union of Pure and Applied Chemistry.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to actinic light and to atmospheric oxygen and other oxidizing agents, preferably by the use of non-actinic glassware and an atmosphere of an inert gas.

Special Reagents—

ETHER—Use *Ether*, page 249, freshly redistilled, discarding the first and last 10-percent portions.

Procedure—Accurately weigh, count, or measure a portion of the sample expected to contain the equivalent of not less than 0.15 mg. of retinol but containing not more than 1 g. of fat. If in the form of capsules, tablets, or other solid, reflux the portion taken in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for about 5 minutes longer.

Transfer to a saponification flask, and add 30 ml. of alcohol if the sample is liquid or 23 ml. of alcohol and 7 ml. of glycerin if the sample is solid, followed by 3 ml. of potassium hydroxide solution (9 in 10). Reflux in an *all-glass* apparatus for 30 minutes. Cool the solution, add 30 ml. of water, and transfer to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract by shaking for 2 minutes with one 150-ml. portion of ether, and, if an emulsion forms, with three additional 25-ml. portions

of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 250-ml. volumetric flask, and add ether to volume.

Evaporate a 25.0-ml. portion of the ether extract to about 5 ml. *Without applying heat and with the aid of a stream of inert gas or vacuum*, continue the evaporation to about 3 ml. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.5 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution at the wavelengths 310 mμ, 325 mμ, and 334 mμ, with a suitable spectrophotometer fitted with matched quartz cells.

WHEN TOCOPHEROL IS PRESENT—Transfer to a saponification flask a suitable sample, accurately measured, or not less than 10 previously crushed Decavitamin Capsules or Decavitamin Tablets. Reflux in an *all-glass* apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (9 in 10) for 30 minutes. Add through the condenser 2.0 g. of hydrous citric acid, washing the walls of the condenser with 10 ml. of water. Cool, and transfer the solution to a conical separator with the aid of 20 ml. of water. Add 2 g. of finely powdered sodium sulfate. Extract with one 150-ml. portion of ether, and, if an emulsion forms, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 250-ml. volumetric flask, and add ether to volume. Transfer a 100.0-ml. aliquot of the resulting ether solution to a conical separator, and wash once with 50 ml. of potassium hydroxide solution (1 in 33), using alcohol, if necessary, to break any emulsion that forms. Wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 100-ml. volumetric flask, and add ether to volume.

Evaporate a 50.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. *Without applying heat and with the aid of a stream of inert gas or vacuum*, remove the residual ether. Dissolve the residue in 50.0 ml. of isopropyl alcohol.

Hydrogenated portion—Pipet 15 ml. of the isopropyl alcohol solution into a 50-ml. centrifuge tube, add approximately 200 mg. of palladium catalyst, stir with a glass rod, and hydrogenate for 10 minutes in a *Hydrogenator* such as is described in the *Alpha Tocopherol Assay*, page 913, using isopropyl alcohol in the blank tube. Add about 300 mg. of chromatographic siliceous earth, stir with a glass rod, and immediately centrifuge until the solution is clear.

Test a 1-ml. aliquot of the solution by removing the solvent by evaporation, dissolving the residue in 1 ml. of chloroform, and adding 10 ml. of antimony trichloride T.S.: no detectable blue color appears. [NOTE—If a blue color appears, repeat the hydrogenation for a longer time period, or with a new lot of catalyst.]

Into two separate flasks pipet equal volumes of the *Hydrogenated portion* and the untreated isopropyl alcohol solution, respectively, and add sufficient isopropyl alcohol to give an expected concentration of vitamin A equivalent to 3 mcg. to 5 mcg. per ml. Determine the absorbances of the untreated solution against the solution from the *Hydrogenated portion* as a blank, at the wavelengths 310 mμ, 325 mμ, and 334 mμ, with a suitable spectrophotometer fitted with matched quartz cells.

Calculation—Calculate the vitamin A content as follows:

$$\text{Content (in mg.)} = 0.549A_{325}/LC,$$

in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule, or tablet in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than $[A_{325}]/1.030$ and not more than $[A_{325}]/0.970$, where $[A_{325}]$ is the *corrected* absorbance at 325 mμ and is given by the equation $[A_{325}] = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$, in which A designates the absorbance at the wavelength indicated by the subscript.

Where $[A_{325}]$ has a value less than $A_{325}/1.030$, apply the following equation:

$$\text{Content (in mg.)} = 0.549[A_{325}]/LC,$$

in which the values are as defined herein.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

Vitamin D Assay

The following procedure is provided for the determination of vitamin D as an ingredient of Pharmacopeial preparations.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to air and to

actinic light, preferably by the use of a blanket of inert gas and low-actinic glassware.

Special Reagents and Solutions—

CHROMATOGRAPHIC FULLER'S EARTH—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

SOLVENT HEXANE—Use solvent hexane (see under *Reagents*), redistilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

ETHYLENE DICHLORIDE—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

POTASSIUM HYDROXIDE SOLUTION—Dissolve 500 g. of potassium hydroxide in water to make 1000 ml.

BUTYLATED HYDROXYTOLUENE SOLUTION—Dissolve 10 mg. of butylated hydroxytoluene in 100 ml. of alcohol. Prepare this solution fresh daily.

COLOR REAGENT—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 20-mm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

FIRST COLUMN—Arrange for descending column chromatography a tube of 2.5-cm. (inside) diameter, about 25 cm. long, and constricted to 8-mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

SECOND COLUMN—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

FIRST COLUMN—To about 125 ml. of isooctane contained in a screw-capped, wide-mouth bottle add 25 g. of chromatographic silicic acid earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

SECOND COLUMN—Pack the midsection of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of U. S. P. Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to give a known concentration of about 250 mcg. per ml. Store in a refrigerator.

On the day of assay, pipet 1 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in, and make to volume with, *Ethylene Dichloride*.

Sample Preparation—Accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 U. S. P. Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 3000 U. S. P. Units) of vitamin A acetate to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g. of the total weight of the sample, but not less than a total of 3.0 ml. Add 10 ml. of *Butylated Hydroxytoluene Solution* and 20 ml. of alcohol. Reflux vigorously on a steam bath for 30 minutes. Cool, and transfer the saponified mixture to a conical separator, rinsing the saponification flask with three 10-ml. portions of water and three 50-ml. portions of ether, adding each rinse to the separator. Add about 1 g. of sodium sulfate decahydrate to the separator,

and extract by shaking for 2 minutes. If an emulsion forms, extract with three 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with additional 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, add ether to volume, and mix. Transfer the entire sample or an accurately measured aliquot containing about 250 mcg. to a tall-form, 400-ml. beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, then decant the solution into a second 400-ml. beaker. Rinse the sodium sulfate with three 25-ml. portions of ether, adding each rinse to the main portion. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with three 10-ml. portions of ether, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation*.

Procedure—

FIRST COLUMN CHROMATOGRAPHY—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column*, pipet 2 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 100 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40° or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane*.

SECOND COLUMN CHROMATOGRAPHY—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column*. Rinse the evaporation flask with a total of 10 ml. of *Solvent Hexane* in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about −125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

ASSAY PREPARATION—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml. volumetric flask, and make to volume with *Ethylene Dichloride* to obtain the *Assay Preparation*.

COLOR DEVELOPMENT—Into each of three suitable, matched colorimeter tubes of about 20-mm. (inside) diameter, and designated *1*, *2*, and *3*, respectively, pipet 1 ml. of the *Assay Preparation*. Into tube *1* pipet 1 ml. of the *Standard Preparation*, into tube *2*, 1 ml. of *Ethylene Dichloride*, and into tube *3*, 1 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add quickly, and preferably from an automatic pipet, 5.0 ml. of *Color Reagent*, and mix. After 45 seconds, accurately timed, following the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes *2* and *3* at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(Cs/C)(Av/As)$, in which Cs is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, Av has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and As has the value of $A^1_{500} - A^3_{500}$ determined on the solution from the *Standard Preparation*.

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NATIONAL FORMULARY XIII

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VITAMIN A ASSAY

Complete the assay promptly and exercise care throughout the procedure to avoid undue exposure to oxidizing agents, to actinic light, and to other conditions that destroy vitamin A. The use of nonactinic glassware is advantageous in avoiding destruction by light.

Isopropyl alcohol—Use *Isopropyl Alcohol*, distil, if necessary to meet the following requirements for spectral purity: when measured in a 1-cm. cell against distilled water it shows an absorbance not greater than 0.05 at 300 mμ and not greater than 0.01 between 320 mμ and 350 mμ.

Ether—Use *Ether*, freshly distilled, discarding the first and last 10 percent portions, or *Ether*, anesthetic grade, from a freshly opened container.

Saponification—Transfer to a saponification flask an amount of the sample, accurately measured and expected to contain not less than the equivalent of 150 mcg. of vitamin A, but not more than 1 g. of fat. Reflux in an *all-glass* apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (1 in 2) for 30 minutes. Cool the solution, add 30 ml. of water, and transfer the resulting solution to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract, by shaking for 2 minutes, with one 150-ml. portion of ether, or, if an emulsion occurs, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously until the last washing gives no color with phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, and dilute to volume with ether.

Procedure—Evaporate a 25.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. Without the application of heat, reduce the volume to about 3 ml. in a stream of inert gas or under reduced pressure. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.4 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution in 1-cm. cells, at 310 mμ, 325 mμ, and 334 mμ with a suitable spectrophotometer, using isopropyl alcohol as the blank.

Calculation—Calculate the vitamin A content as follows: Vitamin A content (in mg.) = $0.549 \times (A_{325}/LC)$, in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule or tablet, in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than $A_{325}(\text{cor.})/1.030$ and not more than $A_{325}(\text{cor.})/0.970$, where $A_{325}(\text{cor.}) = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$, in which A designates the absorbance at the wavelengths indicated by the subscripts. Where $A_{325}(\text{cor.})$ has a value less than $A_{325}/1.030$ apply the following formula: Vitamin A content, in mg., = $0.549[A_{325(\text{cor.})}/LC]$. Each mg. of vitamin A (alcohol)

represents 3333 USP Units of vitamin A.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

VITAMIN D ASSAY

Biological Method

The biological assay of vitamin D comprises the recording and interpretation of observations on groups of rats maintained on specified dietary regimens throughout specified periods of their lives whereby the biological response to the preparation under assay is compared with the response to USP Vitamin D Reference Standard.

Preliminary Period—Throughout the preliminary period in the life of a rat, which is not longer than 30 days and extends from birth to the first day of the depletion period, maintain litters of rats under the immediate supervision of, or according to the directions of, the individual responsible for the assay. During the preliminary period, use a dietary regimen which provides for normal development but is limited in its content of vitamin D, so that when placed upon the *Rachitogenic Diet* in the depletion period the rats develop rickets. At the end of the preliminary period, reject any rat which weighs less than 44 g. or more than 60 g., or which shows evidence of injury, disease, or anatomical abnormality.

Depletion Period—Through the depletion period, which extends from the end of the preliminary period to the first day of the assay period, provide each rat *ad libitum* with the *Rachitogenic Diet* and water and allow access to no other food or dietary supplement.

Rachitogenic Diet—The rachitogenic diet consists of a uniform mixture of the following ingredients in the proportions shown:

	Parts by Weight
Whole Yellow Corn, ground	76
Ground Wheat Gluten	20
Calcium Carbonate	3
Sodium Chloride	1

When a chemical analysis of the entire ration shows a Ca:P ratio of less than 4:1 or more than 5:1, the proportion of calcium carbonate may be varied to bring the adjusted ratio to a uniform level within this range.

Assigning Rats to Groups for the Assay Period—Consider a litter suitable for the assay period when individual rats in the litter show evidence of rickets such as enlarged joints and a distinctive wobbly, rachitic gait, provided that the depletion period is not less than 19 or more than 25 days. The presence of rickets may be established also from the width of the rachitic metaphysis upon X-ray examination or by applying the line test (described below) to a leg bone of one member of each litter.

Record the weight of each rat and assign it to a group, in which each rat will be fed a specified dose of the reference standard or of an assay sample that is under examination for its vitamin D potency. For each assay sample provide one or more assay groups and at least two standard groups. The two standard groups may be used for the concurrent assay of more than one assay sample. Within an interval not exceeding 30 days, complete the assignment of rats to groups according to a design which divides litters among the groups, to achieve a complete balance.

For complete balance, whereby each litter is represented equally in every group, use seven or more litters containing at least as many depleted rats as there are groups. From a given litter, assign one rat, selected at random, to each group on the same day. If a litter contains twice as many rats as there are groups, assign a second series of rats similarly. The last one or two litters to be assigned may be allotted to groups so that at the start of the assay period the average body weight of any completed groups will not differ by more than 8 g. from that of any other group.

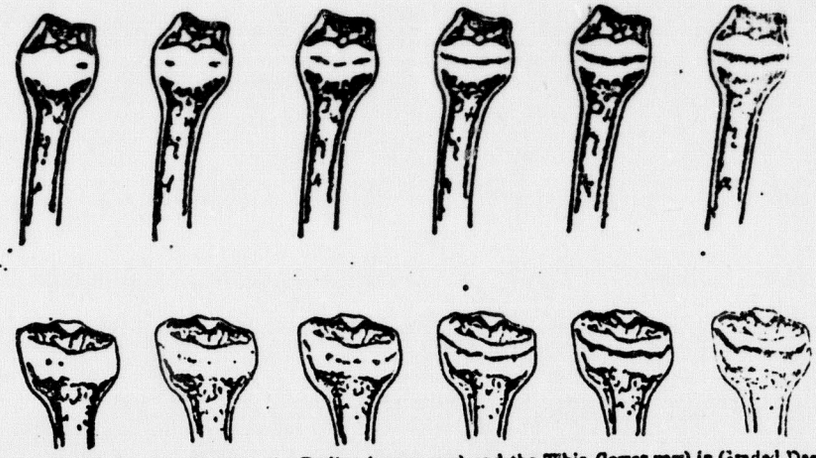
Assay Doses—Select two dosage levels of the USP Vitamin D Reference Standard, spaced so that the ratio of the larger to the smaller dose is not less than 1.5 or more than 2.5. Select one or two dosage levels based upon a single assumed potency for each sample. The dosage levels of the sample are equivalent to those of the standard or to a mid-level equal to the square root of the product of the two dosage levels of the standard.

Select dosage levels such that, when fed to rachitic rats, they are expected to produce degrees of calcification within the range specified under the test of data acceptability. Before feeding, the reference standard and/or sample may be diluted with cottonseed oil, provided that not more than 0.2 ml. is fed on any one day. Store the oil solutions in well-closed bottles, protected from light, at a temperature not exceeding 10°, and use within 5 weeks.

Assign one group of rats to each dosage level of the standard and of the one or more samples.

Assay Period—During the assay period, which extends from the end of the depletion period for a fixed interval of 7 to 10 days, cage each rat individually and provide it *ad libitum* with the *Rachitogenic Diet* and water. Supply a rachitogenic diet prepared from the same lots of ingredients to all rats. On the first and on the third (or fourth) day of the assay period, feed each rat one-half of its total assigned dose.

Throughout the assay period, maintain as uniform environmental conditions as possible for all rats and exclude exposure to



Representative Sections Showing the Radius (upper row) and the Tibia (lower row) in Graded Degrees of Healing in Rachitic Rats within the Useful Range of the Dosage-Response Relationship of the Vitamin D Assay

antirachitic radiations. At the end of a fixed period of 7 to 10 days, weigh and kill each rat. From those rats which do not weigh less at the end than at the start of the assay period and which have consumed each assigned dose within 24 hours of the time it was fed, dissect out one or more leg bones for examination by the *Line Test*.

Line Test—Remove the proximal end of a tibia or the distal end of a radius and clean it of adhering tissue, in any one assay using the same bone from all animals. With a clean, sharp blade cut a median, longitudinal section through the juncture of the epiphysis and diaphysis at the same place on each bone. Rinse both sections in purified water, immerse immediately in silver nitrate solution (1 in 50) for 1 minute, and rinse again in purified water. Expose the cut surface of bone, in water, to daylight or another source of actinic light until the calcified areas develop a clearly defined stain without marked discoloration of the uncalcified areas. The staining procedure may be modified to differentiate more clearly between calcified and uncalcified areas.

Score the degree of calcification of the rachitic metaphysis in each rat, according to a scale which allows the average response to be plotted as a straight line against the logarithm of the dose. The figure presented illustrates the range of the degree of calcification best suited for assay purposes.

Acceptability—Observations are acceptable for use in calculation of the potency only from those groups in which two-thirds or more but not less than 7 rats show calcification at least as great as the lowest level and not greater than the highest level illustrated in the figure. If the average score of the standard group on the high dosage level is not greater than the average score of the standard group on the low dosage level, discard the results and repeat the assay. If an assay sample is represented solely by assay groups which are not acceptable for measuring vitamin D potency and in each of which the average score is less than the average score of the standard group on the low dosage level or more than the average score of the standard group on the high dosage level, its assayed content of vitamin D is respectively less than that represented by the low dose or more than that represented by the high dose of the Reference Standard.

Calculation—Tabulate the scores (y), listing each litter in a separate row with treatment groups in columns. Omit any groups which do not meet the test for *Acceptability*. Equalize the number of observations in the acceptable groups by disregarding the results on all litters not equally represented in the groups or by other suitable means (see *Design and Analysis of Biological Assays*, USP XVIII). Total the f scores for each of the treatment groups, where f is the number of litters, and designate each total as T with subscripts 1 and 2 for the low and high dosage levels, respectively. Compute the slope b from the sums of T_1, *i.e.*, ΣT_1, and of T_2, *i.e.*, ΣT_2, for the standard and sample, provided the latter is represented at both dosage levels as $b = (\Sigma T_2 - \Sigma T_1)/ih'$, where i is the logarithm of the ratio of the high dose to the low dose and is the same for each preparation, and h' is the number of preparations represented by two dosage levels and included in the calculation of the value of b.

Compute the logarithm of the relative potency of each sample under assay as log (relative potency) $= M' = (\bar{y}_U - \bar{y}_S)/b = ih'T_s/2\Sigma T_s$, where each mean score, $\bar{y}_U$ for the assay sample and $\bar{y}_S$ for the Reference

Standard, is the average of the individual scores for an intermediate dosage level or of the two means for the high and the low dosage levels and where $T_b = \Sigma T_2 - \Sigma T_1$ and T_e is defined in USP XVIII. Convert each observed M' to its antilogarithm to obtain the relative potency of the sample. Multiply the relative potency by the assumed potency of the assay oil in Units per g., adopted at the start of the assay, to obtain its assayed content of vitamin D in USP Units per g.

Chemical Method

The following procedure is provided for the determination of vitamin D as an ingredient of official preparations containing other active constituents.

Special Reagents and Solutions—

Chromatographic Fuller's Earth—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

Solvent Hexane—Use reagent solvent hexane (see USP XVIII), distilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

Ethylene Dichloride—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

Potassium Hydroxide Solution—Dissolve 780 g. of potassium hydroxide in water to make 1000 ml.

Cottonseed Oil—Use cottonseed oil USP that meets the following additional requirement: Saponify 10 g. of the oil as directed in this chapter under *Sample Preparation*, beginning with "then add a volume of *Potassium Hydroxide Solution*," and dissolve the unsaponifiable residue in 10 ml. of *Solvent Hexane*.

In a separate container place 0.4 ml. of ferric chloride solution (1 in 1000) and 12 ml. of a 1 in 6000 solution of 2,2′-bipyridine in dehydrated alcohol, mix, and 5 minutes later read the absorbance in a 1-cm. cell at 520 mμ, with a suitable spectrophotometer, using dehydrated alcohol as the blank. Then add 0.2 ml. of the solvent hexane solution of the unsaponifiable residue, and after 5 minutes read the absorbance. The difference between the first and the second absorbances is not less than 0.125.

Color Reagent—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered, container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 2-cm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

First Column—Arrange for descending column chromatography (see page 786) a tube of 2.5 cm. (inside) diameter, about 25 cm. long, and constricted to 8 mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

Second Column—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

First Column—To about 125 ml. of isooctane contained in a screw-cap, wide-mouth bottle add 25 g. of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

Second Column—Pack the midsection of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of USP Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to make 100.0 ml. Store in a refrigerator.

On the day of assay, pipet 1.0 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in, and dilute to volume with, *Ethylene Dichloride*.

Sample Preparation—Unless otherwise

directed, accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 USP Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 5000 USP Units) of vitamin A to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add 2 ml. of *Cottonseed Oil*, then add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g. of the total weight of the sample plus cottonseed oil, but not less than 15 ml. Add 50 ml. of alcohol. Reflux vigorously on a steam bath for 20 minutes, or for 30 minutes for samples weighing more than 5 g. If oil globules are evident, indicating incomplete saponification, add 5 ml. of *Potassium Hydroxide Solution* (but not exceeding a total of 100 ml.), and heat again. Cool, and transfer the saponified mixture to a 500-ml. separator, rinsing the saponification flask with a total of 50 ml. of water and adding each rinse to the separator. Add about 4.5 g. of sodium sulfate decahydrate and 150 ml. of *Solvent Hexane*. Shake vigorously for 2 minutes. When the aqueous layer has separated, transfer it to a second separator. Extract with two 50-ml. portions of *Solvent Hexane*, combine the extracts, and discard the aqueous solution.

Wash the combined solvent hexane extracts with 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Allow the washed extract to stand for 5 minutes, discard any water that separates, and transfer the extract to a 300-ml. tall form beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, and decant the solution into a 500-ml., tall-form beaker. Rinse the sodium sulfate with four 25-ml. portions of *Solvent Hexane*, combining the rinsings with the original extract. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with four 5-ml. portions of *Solvent Hexane*, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation*.

Procedure—

First Column Chromatography—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column*, pipet 2.0 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 100 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane*.

Second Column Chromatography—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column*. Rinse the evaporation flask with a total of 10 ml. of solvent hexane in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about 125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

Assay Preparation—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml. volumetric flask, and dilute to volume with *Ethylene Dichloride* to obtain the *Assay Preparation*.

Color Development—Into each of three suitable, matched colorimeter tubes of about 2-cm. diameter, and designated *1*, *2*, and *3*, respectively, pipet 1.0 ml. of the *Assay Preparation*. Into tube *1* pipet 1.0 ml. of the *Standard Preparation*, into tube *2*, 1.0 ml. of *Ethylene Dichloride*, and into tube *3*, 1.0 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add quickly, and preferably from an automatic pipet, 3.0

ml. of *Color Reagent*, and mix. Exactly 45 seconds after the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes *2* and *3* at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(C_S/C) \times (A_U/A_S)$, in which C_S is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, A_U has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and A_S has the value of $A^1_{500} - A^3_{500}$ determined on the solution from the *Standard Preparation*.

AFFIDAVIT OF STEPHEN A. McNAMARA

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION AND SOLGAR CO, INC.,

Plantiffs,

-against-

F. DAVID MATHEWS, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

AFFIDAVIT

73 Civ. 3448 MEF

STATE OF MARYLAND)
COUNTY OF MONTGOMERY)

STEPHEN HULL McNAMARA, Associate Chief Counsel for Food, United States Food and Drug Administration, first being duly sworn, deposes and says:

1. In a conference in chambers on September 4, 1975, the Court directed that all documents that should properly be considered part of the record of the administrative proceeding which led to the promulgation of the regulations under attack in this case (and that have not already been provided) be assembled and filed with the Court.

2. Pursuant to the conference with the Court on September 4, 1975, an intensive search has been made of internal Agency files in an attempt to find any additional material that might have been before the Commissioner at the

time he determined to adopt the regulations at issue in this case. We have found a number of documents, perhaps two hundred pages in all (including duplicative materials in more than one internal file), which fall generally into the following categories: (a) "action memoranda" to the Commissioner recommending promulgation of the regulations; (b) early working drafts of the documents ultimately published in the Federal Register; (c) letters to the Agency by physicians expressing concern about the toxicity of vitamins A and D; (d) memoranda between personnel in the Agency regarding the regulations; (e) copies of articles from various periodicals; and (f) some fairly cursory records of meetings on the subject.

3. Although additional documents have been located, the Food and Drug Administration submits that the Court has already been provided with all documents that should properly be considered to comprise the record of the administrative proceeding, i.e., all documents included or incorporated by reference in the official public file compiled by the Food and Drug Administration Hearing Clerk in this rulemaking proceeding. These documents include the Federal Register document that proposed the promulgation of the regulations, copies of medical publications cited in the bibliography that accompanied the proposal, copies of all

comments received in response to the proposal, and the Federal Register document promulgating the final regulation.

4. The Food and Drug Administration submits that (at least in the absence of extraordinary circumstances not present here) Agency regulations issued pursuant to Section 701(a) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 371(a), and Section 4 of the Administrative Procedure Act, 5 U.S.C. 553, should stand or fall on the record described in paragraph (3). Such an approach is fair and reasonable in that (a) all persons have the opportunity to file any comments (data, briefs, or other documents) that they wish to be included in the record and considered by the Agency during the rulemaking proceeding; (b) all submissions by the public and all other materials on which the Agency relies in promulgating its regulations are available in the Hearing Clerk's file for public scrutiny and comment; (c) a reviewing court has a finite and closed record to examine in determining whether the Agency's regulations are arbitrary, capricious, or otherwise not in accordance with law; and (d) judicial review is properly defined in that both sides are foreclosed from offering additional evidence before a reviewing court that should have been made available to, or adduced by, the Agency (and included in the Hearing Clerk's file for public scrutiny and comment) during the course of the rulemaking proceeding.

5. In addition to the Agency's position that the additional documents located are not properly part of the record, we believe that some of the documents are privileged from disclosure in that they reflect the internal deliberative processes of the Agency. Furthermore, since established principles of administrative law counsel against inquiry into the mental processes of the Agency head, as this Court recognized in denying a request for a deposition of the Commissioner at the outset of this case, it would seem clear that memoranda reflecting the mental processes of subordinates who are not themselves the ultimate decision-maker are inappropriate for release to the public on the pretext of their being part of the rulemaking record.

6. We would willingly make these additional documents available for in camera inspection, should the Court determine that further inquiry is warranted. And, of course, we would provide all the documents as a part of the "record", should the Court so rule. (The documents have already been lodged with Assistant United States Attorney Naomi Reice Buchwald, should the Court wish to examine them.)

7. Therefore, we urge the Court to rule that the entire administrative record is now before it. Furthermore, in this regard, a memorandum will be submitted to the

Court on the record now before it. We submit that this record is more than sufficient to withstand the claim that the regulations are arbitrary, capricious, or otherwise not in accordance with law, without any additional testimony, by affidavit or otherwise, or additional "record" evidence.

Stephen H. McNamara

Stephen Hull McNamara
Associate Chief Counsel for Food
United States Food and Drug Administration

Subscribed and sworn to before me, a Notary Public, this 30th day of October, 1975.

Grace L. Edwards

Notary Public

My commission expires July 1, 1978.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.	:	
Plaintiffs	:	73 Civ. 3448
v.	:	
F. DAVID MATHEWS, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,	:	AFFIDAVIT
Defendants	:	

County of Montgomery)
State of Maryland)

Alexander M. Schmidt, M.D., Commissioner of Food and Drugs, first being duly sworn, deposes and says:

(1) In the Federal Register of August 2, 1973, 38 F.R. 20723-20725, I promulgated final regulations for the United States Food and Drug Administration which provide that high dosage preparations of vitamins A and D, as specified in the regulations, are deemed to be prescription drugs. These regulations currently appear in Title 21 of the Code of Federal Regulations, Section 250.109 and 250.110 (21 CFR 250.109 and 250.110). (These regulations were formerly codified at 21 CFR 3.94 and 3.95.) Copies of the notice of proposed rulemaking, a subsequent correction, and the final regulations, as published in the Federal Register, are attached.

(2) I have now read the decision of the United States Court of Appeals for the Second Circuit, captioned National Nutritional Foods Assn. v. Weinberger, 512 F.2d 688 (2d Cir. 1975), and it is my understanding that the Court of Appeals has upheld our regulations in all respects but one, i.e., it has remanded the case to the United States District Court for the Southern District of New York for specific inquiry into the basis on which I concluded that high dosage oral preparations of vitamins A and D are "drugs". My lawyers have advised me that I should accordingly explain in detail my basis for categorizing these products as drugs.

(3) At the outset, I want to make clear that I am familiar with the definition of the term "drug" contained in Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(g)(1), and that I believe the high dosage vitamin A and D products subject to these regulations come within this definition:

> The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clauses (A), (B), or (C) of this paragraph; but does not include devices or their components, parts, or accessories.

(4) Speaking frankly, I believe we did not set forth a more detailed rationale for the drug status of these high dosage preparations in the Federal Register of August 2, 1973, because we felt the classification was so obviously proper. When I promulgate a regulation concerning labeling or composition for articles which I know to be recognized in the United States Pharmacopeia and in the National Formulary, which are being sold in the form of pills and capsules, which I know -- from my experience as a practicing physician and as a medical school dean and more recently as Commissioner of Food and Drugs -- are being widely prescribed by physicians for the treatment of serious disease conditions, and which are too potent and toxic to be useful for ordinary nutritional purposes, I simply do not pause for long over the issue of whether such articles are drugs. Similarly, if I were promulgating today a regulation concerning the labeling of an oral penicillin product, or a polio vaccine to be dispensed on a sugar cube, I would not seriously pause for long over some objection that such products were "foods". In any event, I shall now proceed to explain, to the best of my memory, why I concluded then, and would conclude now, that high potency vitamin A and D preparations are drugs.

(5) Section 201(g)(1)(B) of the Act, 21 U.S.C. 321(g)(1)(B), provides that the term "drug" includes "articles intended for use in the ... cure, mitigation, treatment, or prevention of disease ..." In National Nutritional Foods Assn. v. FDA, 504 F.2d 761, 789 (2d. Cir. 1974),

Judge Friendly observed that under Section 201(g)(1)(B) an article may be deemed to be a drug, in spite of a manufacturer's "subjective" claims of other intent, if the "objective evidence" demonstrates therapeutic intent.

Pursuant to Judge Friendly's ruling, it seems to me that it is reasonable and proper to categorize high dosage preparations of vitamins A and D as drugs because these preparations, viewed objectively, are intended for therapeutic usage. Indeed, our notice of proposed rule making in the Federal Register specifically took note of "widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders".

I have long been aware of the numerous and widespread therapeutic usages for these products. For example, high dosages of vitamin A, exceeding 10,000 IU and ranging up to 100,000 IU per day, depending upon the condition, are used in the treatment of severe primary vitamin A deficiency and xerophthalmia, and of diseases and disorders which interfere with absorption of vitamin A, e.g., biliary cirrhosis of the liver, sprue, cystic fibrosis, infantile and adult celiac disease, and biliary obstruction. High dosages of vitamin A have also been used as an anti-infective agent for prevention of renal calculi, and in the treatment of acne, hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn, and cutaneous ulcerative conditions -- although evidence is lacking to demonstrate efficacy for these usages.

High dosages of vitamin D, exceeding 400 IU and ranging up to 800,000 IU per day, depending upon the condition, are used in the treatment of, e.g., ordinary rickets, vitamin D resistant rickets, hypoparathyroidism, infantile tetany, a group of diseases characterized by intestinal malabsorption, e.g., severe gluten enteropathy, and diseases that affect the bone and kidneys, e.g., familiar hypophosphatemias, the Fanconi syndrome, and chronic uremia. Large doses may be required in patients with successful kidney transplants. High dosages of vitamin D have also been used in the treatment of psoriasis, arthritis, and hay fever (although the rationale of therapy for these last three usages is subject to serious question).

In any of these cases involving large doses of vitamin A and D, extreme care is required to adjust, and frequently readjust, doses to obtain maximal therapeutic benefit while keeping toxic effects as low as possible.

It seems to me that the seller of such a high potency vitamin A or D preparation, which exceeds the levels recognized to be useful for ordinary nutritional supplementation, knows or should know that his product is likely to be used by purchasers hoping for some therapeutic benefit such as deliverence from cirrhosis, acne, psoriasis or arthritis. Frankly, it makes no more sense to me that someone should be able to say that such a product is not a drug because he subjectively wants to eat it as a food than it would to allow distributors of aspirin or LSD to avoid regulation of their products as drugs by saying that they have some customers who like the taste and who subjectively choose to regard these articles as foods.

(6) Section 201(g)(1)(A) of the Act, 21 U.S.C. 321(g)(1)(A), provides that the term "drug" includes "articles recognized in the official United States Pharmacopeia ... or official National Formulary ..." Vitamins A and D were recognized in the United States Pharmacopeia and in the National Formulary at the time of promulgation of the regulations, and the vitamins continue to be recognized in the current editions of these drug compendia. Copies of relevant pages of United States Pharmacopeia XVIII and National Formulary XIII (in effect at the time of promulgation of the regulation) and United States Pharmacopeia XIX and National Formulary XIV (in effect at the present time) are attached to my affidavit.

I agree with Judge Friendly's statement in the case of National Nutritional Foods Association v. FDA, 504 F.2d 761, 789 (2d. Cir. 1974), that it "would prove too much" to say that all vitamin preparations are drugs simply because vitamins are recognized in the U.S. Pharmacopeia or the National Formulary. However, it is not necessary to reach Judge Friendly's reductio ad absurdum under which all vitamins and minerals might arguably be classified as drugs because they appear in an official compendium.

Unlike most articles recognized in the U.S. Pharmacopeia and the National Formulary, which are included because of therapeutic usage, vitamins A and D are specifically recognized in the U.S.P. and N.F. for prophylactic (food) usage as well as for therapeutic (drug) usage. In my judgment, while the Act provides that an article is deemed to be a drug if "recognized" in the U.S.P. or N.F., a vitamin preparation should nevertheless not be classified as a drug on this basis with respect to a

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usage which is specifically recognized by these compendia to be a prophylactic (food) usage. Consistent with this principle, the vitamin preparations subject to the regulations exceed the levels of potency recognized as "prophylactic" in the United States Pharmacopeia and National Formulary (both in the editions in effect at the time of promulgation of the regulations and in the editions presently in effect).

In sum, in the context of high potency vitamin A and D preparations, it does not seem to me to "prove too much" to say that their recognition in the United States Pharmacopeia and National Formulary is sufficient to confirm, if not to establish, their drug status. Such application of the language of 21 U.S.C. 321(g)(1)(A) would not result in all vitamin A and D preparations being "drugs."

Nor does it seem unreasonable for me as Commissioner of Food and Drugs, charged with the enforcement of the Federal Food, Drug, and Cosmetic Act, to take note that, in the absence of therapeutic claims, the "food" definition in 21 U.S.C. 321(f) fairly applies to lower dosages of vitamins A and D, which possess nutritional usefulness, and to decide that in view of the existence of two definitions applicable to preparations of vitamins A and D, I will, in the interest of efficient enforcement of the law, restrict the drug definition (in the absence of therapeutic claims for a lower potency product) to high potency preparations which are inappropriate for nutritional use and which possess a real potential for human harm.

(7) I am aware of Judge Friendly's statement in National Nutritional Foods Assn. v. FDA, 504 F.2d 761, 789 (2d. Cir. 1974) (reviewing 21 CFR 125.1(h) and not the present vitamin A and D regulations) that "demonstrated uselessness as a food for most people" is not a sufficient basis for my declaring all such articles to be drugs. Whatever the merits of 21 CFR 125.1(h), it seems clear to me that much more than "demonstrated uselessness as a food for most people" is involved in the drug determination in the present vitamin A and D regulations. The situation is much more extreme. These high potency vitamin A and D preparations provide excessive amounts of the vitamins which are useless as a food for virtually anyone unless he is suffering from a serious disease condition requiring continuing medical supervision, in which case carefully selected quantities of the vitamin(s) are used as part of the total therapy of the patient.

Furthermore, the levels involved in the vitamin A and D regulations pose a dangerous potential for harm. In promulgating these regulations, concern over the public harm that could be done by these high potency therapeutic preparations weighed more heavily upon my mind than any other single factor.

The notice of proposed rule making listed in considerable detail the various types of harm that people can do to themselves, or to their children, or to an unborn fetus, by overdosing with these vitamins. Among the adverse effects from excessive intake of vitamin A to which our notice referred were: anorexia, growth retardation in children, drying and

cracking of the skin, hepatosplenomegaly, increased intra-cranial pressure, alopecia, migratory arthralgia, bone pain, hypomenorrhea, irritability, and headache.

Noting that "[g]enerally, the margin of safety between nutritional requirements and toxic levels is small for vitamin D", we detailed the consequences of hypervitaminosis D:

> [A]norexia, nausea, weakness, weight loss, polyuria, constipation, vague aches, stiffness, generalized vascular, soft tissue and premature epiphyseal calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure and death.
>
> ***
>
> There is good evidence suggesting that the supravalvular aortic stenosis syndrome with hypercalcemia in infants and children may result from excess intakes of vitamin D by the infant and/or by the mother during pregnancy. This latter syndrome may have a tragic outcome with severe aortic stenosis, mental and physical retardation, elfin facies, renal failure and death.

Indeed, I note that even the Court of Appeals apparently had no serious doubts about the potential for harm in view of the Court's statement at 512 F.2d 704 that:

> There was ample evidence before the FDA that Vitamins A and D, when consumed in large quantities over a period of time, can be acutely toxic. It was reasonable for the Commissioner to recognize that the risks of toxicity are increased by over-the-counter availability of readily ingestible, high dosage forms, and therefore he could rationally conclude that these forms have a "potential harmful effect."

In sum, unlike the circumstances addressed by Judge Friendly, far more than "demonstrated uselessness as a food for most people" is involved here. In the case of these high potency vitamin A and D preparations, we have demonstrated uselessness as a food for virtually anyone not suffering from a serious disease or disorder requiring continuing medical supervision, as well as (1) a dangerous risk of harm to the public health, (2) widespread use for therapeutic purposes (see paragraph 5 of this affidavit) and (3) recognition in the United States Pharmacopeia and in the National Formulary (see paragraph 6 of this affidavit).

(8) Of course, explicit therapeutic claims made for a product in its labeling, advertising, etc., would cause an article to be deemed a drug regardless of its actual potency. 21 U.S.C 321(g)(1)(B).

(9) In addition to protection of the public from the toxic effects of overdosing, classification of these high potency products as drugs (and consequently, because of their potential for harm, as prescription drugs) would redound in other ways to the benefit of the public health. For example:

(a) Our Food and Drug Inspectors, upon conducting a factory inspection, are entitled to demand production of master formula records, batch production records, reports of analyses and other quality control records if these products are prescription drugs, but not if the products are foods. 21 U.S.C. 374(a). Such records are very helpful in assuring, e.g., that

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potent ingredients are evenly dispersed, in the labeled amount, throughout a batch of tablets.

(b) Persons who produce drugs must register their names and addresses with the Food and Drug Administration on a yearly basis, which facilitates our regular inspection of all such persons; persons who deal in foods are not subject to this requirement. 21 U.S.C. 360.

(c) If drugs, these products are subject to comprehensive drug good manufacturing practice ("GMP") regulations, which address directly the methods of manufacture involved in the production of vitamin preparations, 21 U.S.C. 351(a)(2)(B), 21 CFR 133.2-133.15, while if foods they are subject to the more general food GMP regulations which are not designed to provide the same precision of control of ingredients. 21 CFR 128.

(10) Moreover, it would serve no useful purposes to recognize in the regulations a hypothetical food use of such high dosage oral preparations of vitamins A and D because any such food use would be illegal. The Court of Appeals has already recognized that, if classified as drugs, these high dosage oral preparations pose such a potentiality for public harm that the Food and Drug Administration may properly restrict their availability to prescription sale. Because this potential for harm exists, such high potencies of vitamin A and D would lack general recognition of safety for inclusion as components in a preparation intended for over-the-counter sale as a food to laymen, and would thus be food additives within the meaning of 21 U.S.C. 321(s). Since there is no exemption or regulation

permitting such food additive use, such a food additive usage would be deemed to be unsafe pursuant to 21 U.S.C. 348(a) and any finished preparation containing such levels would accordingly be deemed to be adulterated pursuant to 21 U.S.C. 342(a)(2)(C). Surely any rational person would agree that a potent ingredient which causes a preparation not to be safe for use except under the supervision of a physician, and which thus causes the preparation to be a prescription drug if classified as a drug, would perforce lack general recognition of safety for inclusion in a food preparation intended for sale in grocery stores, and would thus be deemed a food additive for any such food use within the meaning of 21 U.S.C. 321(s). In sum, it appears to me that there would be no point in recognizing in the regulation a hypothetical food usage which would be illegal; indeed, the illegality of any such food usage is implicit in the issuance of a prescription drug regulation.

(11) I reiterate my judgment that restriction to prescription drug status of these high dosage oral preparations of vitamins A and D is essential for the protection of the public health, and my conclusion that these high dosage preparations are properly classed as "drugs".

A. M. Schmidt.

Alexander M. Schmidt, M.D.
Commissioner of Food and Drugs

Sworn and subscribed to before me this 13th day of February, 1975, at Rockville, Maryland.

Grace L. Edwards

Notary Public

My Commission Expires July 1, 1978.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

VITAMIN A AND VITAMIN D

Proposed Statement of Policy

Large doses of vitamin A and/or vitamin D ingested over long periods of time can cause adverse effects, some of which are serious. Vitamins A and D are fat-soluble and excess quantities accumulate in fatty tissue. The acute and chronic toxicity of these vitamins is documented extensively in the medical literature. Vitamin A is available over the counter in dosage levels up to 10 times the recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council (NAS-NRC), and vitamin D is available up to 60 times the RDA. The availability without prescription of these vitamins in high dosage levels contributes significantly to their misuse and the occurrence of serious adverse effects.

In view of the toxicity of excessive quantities of these vitamins, it is of concern to the Food and Drug Administration and medical authorities that there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders. In its "Newsletter" of June 1, 1972 (Vol. 23, No. 9), the American Academy of Pediatrics (AAP) comments on the critical dangers of use of high doses of vitamin A that have been recommended in the lay press, on radio, and on television. For example, the layman is being advised that he would profit from taking 25,000 International units (IU) of vitamin A with [illegible] of vitamin D, or twice these amounts, daily.

The AAP Committees on [illegible] Nutrition published a joint committee statement entitled "The Use and Abuse of Vitamin A" in the journal "Pediatrics," Volume 48, Number 4, October 1971, warning physicians regarding vitamin A toxicity. This article states: "Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through easy availability of high potency vitamin preparations without prescription and by the overzealous parents who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods." The AAP Committee on Drugs specifically has urged the Food and Drug Administration to limit the potency of vitamin A preparations available over the counter.

There exists considerable information in the literature regarding these vitamins and their toxicity. A listing of a number of pertinent articles, many of them recent, regarding these vitamins has been placed on file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852 for public view.

The highlights regarding toxicity of vitamins A and D and the [illegible] for limiting over-the-counter availability of these vitamins are as follows:

VITAMIN A

Adverse effects which result from excess intake of vitamin A [illegible] growth retardation in children, [illegible] and cracking of the skin, hepatosplenomegaly, increase intracranial pressure, alopecia, migratory arthralgia, bone pain

hypomenorrhea, irritability, and headache. Doses of 50,000 IU in adults and 20,000 IU in infants on a daily basis over long periods are known to produce toxicity. At present vitamin A is available over the counter in dosage levels as high as 50,000 IU per dosage unit. In recent years, some physicians and laymen have used large doses of vitamin A in the treatment of acne, although such therapy has not been shown to be safe and effective. Vitamin A in excessive dosages is used over long periods of time for this indication. Adverse effects, particularly increased intracranial pressure which may mimic a brain tumor, have been observed in children and young adults who are receiving vitamin A therapy for the treatment of acne. Reports of such effects have been published in the medical literature.

The position of the AAP on the matter is clear, as cited above.

In the United States, the Food and Nutrition Board, NAS/NRC, is the recognized authority for determining vitamin and other nutritional requirements for the human. The recommended daily dietary allowances (RDA) of the Food and Nutrition Board for vitamin A are 1,500 IU for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for older children and adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

Based on the above considerations, it is the opinion of the Food and Drug Administration and medical experts that preparations containing vitamin A in excess of 10,000 IU per dosage unit shall be dispensed only by prescription and that for any vitamin A preparation intended for distribution as a dietary supplement or as an over-the-counter drug, the recommended daily dosage shall not exceed 10,000 IU vitamin A.

VITAMIN D

There are marked differences in tolerances to Vitamin D in humans when quantities in excess of normal requirements are ingested over prolonged periods. There are significant numbers of individuals who are hyperreactive to excess vitamin D. Generally, the margin of safety between nutritional requirements and toxic levels is small for vitamin D. The margin is particularly small in those individuals who are hyperreactive.

In infants, children and adults, excessive ingestion of vitamin D results in hypervitaminosis D characterized by anorexia, nausea, weakness, weight loss, polyuria, constipation, vague aches, stiffness, generalized vascular, soft tissue and premature epiphyseal calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure and death.

Daily ingestion by infants of doses between 1,000 and 2,000 IU has produced hypervitaminosis D, usually manifested as the infantile hypercalcemia syndrome. There is good evidence suggesting that the supravalvular aortic stenosis syndrome with hypercalcemia in infants and children may result from excess intakes of vitamin D by the infant and/or by the mother during pregnancy. This latter syndrome may have a tragic outcome with severe aortic stenosis, mental and physical retardation, elfin facies, renal failure and death.

The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin D for all age groups for which the vitamin is required is 400 IU. Although a daily intake of 400 IU of vitamin D is sufficient to prevent vitamin D deficiencies, preparations are available over the counter in dosage levels up to 25,000 IU per dosage unit. Excessive dosages of vitamin D have also been promoted in the lay press as noted above.

Based on the toxicity of vitamin D, the possibility of severe irreversible adverse effects in some instances, and the narrow margin of safety, it is the consensus of medical experts and the Food and Drug Administration that preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed only by prescription and that the recommended daily dosage of any vitamin D preparation marketed as a special dietary food or as an over-the-counter drug shall not exceed 400 IU.

Therefore, because of the toxicity of vitamins A and D, their continued promotion in high doses to the lay person, and the continuing reports of adverse effects attributable to excessive intake of these vitamins, the FDA concludes it is in the interest of consumer safety to take the action herein described.

All vitamins are included among the over-the-counter drugs to be reviewed by an OTC Drug Advisory Review Panel, under the procedures established in the FEDERAL REGISTER on May 11, 1972 (37 F.R. 9464). Safety and effectiveness and more general questions related to adequate labeling of vitamin preparations marketed as OTC drugs will be considered by that panel, as well as the differences between foods for special dietary use, OTC drugs, and prescription drugs as they relate to vitamins. The Food and Drug Administration will publish, in the near future, new regulations governing dietary supplements of vitamins and minerals. Until such time as the OTC Drug Advisory Review Panel has completed its review and the new regulations for dietary supplements of vitamins and minerals are in effect, the Food and Drug Administration will not object to the inclusion in vitamin products marketed as foods for special dietary use or as OTC drugs of vitamin D at levels not exceeding 400 IU per dosage unit or 10,000 IU of vitamin A per dosage unit and with the recommended daily dosage not exceeding 400 IU of vitamin D or 10,000 IU of vitamin A.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502 (a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352 (a), (f), and (j), 353 (b), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes to amend Part 3 by adding the following new sections:

§ 3.— Vitamin A preparations for oral use as drugs.

(a) Vitamin A is clearly known to be an essential nutrient for humans. Large doses of vitamin A can cause adverse effects, some of which are serious. The toxicity of vitamin A is well documented in the medical literature. The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin A are: 1,500 international units (IU) for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

(b) In view of the toxicity from the use of large doses of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(3) The recommended daily dosage of vitamin A does not exceed 10,000 IU.

(c) Vitamin A preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final publication in the FEDERAL REGISTER).

§ 3.— Vitamin D preparations for oral use as drugs.

(a) The importance of vitamin D in human nutrition is established. It is also widely recognized that vitamin D, when ingested daily in excessive amounts, is toxic. The recommended daily dietary allowance of vitamin D established by the Food and Nutrition Board, National Academy of Sciences-National Research Council for the prevention of vitamin D deficiency for all age and physiological groups for which the vitamin is required is 400 IU from all sources.

(b) In view of the known toxicity and seriousness of the adverse effects that may be caused by excessive consumption of vitamin D, the Food and Drug Administration finds that in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appro-

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priate warnings regarding vitamin D toxicity.

(3) The recommended daily dosage of vitamin D does not exceed 400 IU.

(c) Vitamin D preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER).

Interested persons may, within 60 days after publication thereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding these proposals. Comments may be accompanied by a memorandum or brief in support thereof. Comments received will be available for public inspection at the above office during regular business hours, Monday through Friday.

Dated: November 28, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.72-21379 Filed 12-13-72;8:45 am]

393a

PROPOSED RULE MAKING

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

VITAMIN A AND VITAMIN D

Proposed Statement of Policy; Correction

The Commissioner of Food and Drugs issued a proposed statement of policy on the use of vitamin A and vitamin D which was published in the FEDERAL REGISTER of Thursday, December 14, 1972 (37 FR 26618). The provisions of the proposed new sections should be corrected as follows:

1. The proposed § 3.—— *Vitamin A preparations for oral use as drugs* is amended by deleting paragraph (b)(3), redesignating paragraph (c) as paragraph (d), and adding a new paragraph (c) to read as set forth below.

§ 3.—— Vitamin A preparations for oral use as drugs.

• • • • • •

(b) • • •

(3) [Deleted]

(c) Preparations containing 10,000 or less I.U. of vitamin A per dosage unit will be regarded as misbranded if their recommended daily dosage exceeds 10,000 I.U.

• • • • • •

2. The proposed § 3.—— *Vitamin D preparations for oral use as drugs* is amended by deleting paragraph (b)(3), redesignating paragraph (c) as paragraph (d), and adding a new paragraph (c) to read as set forth below.

§ 3.—— Vitamin D preparations for oral use as drugs.

• • • • • •

(b) • • •

(3) [Deleted]

(c) Preparations containing 400 or less I.U. of vitamin D per dosage unit will be regarded as misbranded if their recommended daily dosage exceeds 400 I.U.

• • • • • •

Dated: December 26, 1972.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.73-132 Filed 1-3-73;8:45 am]

Approximately 2,500 comments and 1,000 signatures on petitions were received in response to the proposal. Comments were received from a wide segment of the public, including individual consumers, physicians, nurses, pharmacists, dietitians, home economists, nutritionists, nine pharmaceutical manufacturers, a number of vitamin preparation distributors, and health food store operators. Comments from the medical profession were presented by the American Academy of Pediatrics and the American Medical Association. Organized consumer groups that responded were the National Health Federation, Oregon Student Public Interest Research Group, Committee Against Health Fraud, Inc., Committee for the Cessation of "Fortification" of Food Products with Calciferol Hormones, Virginia Citizens Consumer Council, Inc., Consumers Cooperative of Berkeley, Inc. Comments were also submitted by the Wisconsin Alumni Research Foundation, The Ann Arbor Dietetic Association, the American Dietetic Association, and five trade associations: The Pharmaceutical Manufacturers Association, East Coast Health Food Corporation, the National Food, Drug and Cosmetic Association of Manufacturers and Distributors, Inc., the National Nutritional Foods Association and the National Association of Pharmaceutical Manufacturers.

General Comments

The proposal was controversial and generated widely ranging comments regarding broad issues raised by the use of vitamins in foods and drugs. Many of these comments are not appropriate for consideration of the more limited issues raised in the proposed regulation regarding vitamin A and vitamin D. With respect to the broad issues of vitamin and mineral use the Commissioner notes that several regulations including comprehensive discussion of these issues have been published in the FEDERAL REGISTERS of January 19 and March 14, 1973 (38 FR 2124, 6950) and elsewhere in this issue of the FEDERAL REGISTER.

The majority of responses from individual consumers were opposed to the proposal. In reviewing such comments, the Commissioner is concerned that the public is not fully aware of the provisions and medical basis of the proposal. For example, the tenor of many comments was that vitamin A and vitamin D would be available only on prescription. Form letters and several petitions, which were submitted with a number of signatures, contained key statements, presumably the basis on which the signatures were obtained, that bear very little, if any, resemblance to the actual provisions of the proposal. It is clear that the majority of individual consumers responding had been improperly or inadequately informed.

The comments fall into three general categories:

(1) Those who agree that the action proposed by the Food and Drug Administration is necessary and that the prescription levels proposed for vitamin A and vitamin D are suitable. Those who agreed included the American Academy of Pediatrics, the American Medical Association, the American [illegible] Association, five consumer groups, a number of physicians, dietitians, nutritionists, home economists and other professionals in the scientific and health care community, and a few individual consumers.

(2) Those who agree that such vitamins can be toxic, but only at levels higher than those levels proposed by the Food and Drug Administration. The majority of the drug manufacturers and trade associations, and some consumers made responses that were in this category.

(3) Those who disagree with the proposal entirely, stating that such vitamins are foods and that individuals should have the right to ingest any amount desired. The comments from most individual consumers, operators of health food establishments and a consumer group were in this category.

Specific Comments

1. A number of comments contended that "natural" vitamins [illegible] vitamin A and vitamin D) and minerals are foods rather than drugs and should not be treated as drugs. Some viewed "natural" vitamins as safe whereas synthesized vitamins may be (or are) toxic.

The question regarding whether a vitamin is a food or drug generated considerable discussion. The [illegible] and final orders promulgating [illegible] and 125.3 (21 CFR 80.1, 125.1 [illegible]), published in the January [illegible] FEDERAL REGISTER (38 FR 2150, [illegible] elsewhere in this issue of the FEDERAL REGISTER discuss this matter in detail. The Commissioner concludes, on the basis of all the available evidence, that vitamins between the upper and lower limits as specified in § 80.1 are adequate for all known nutritional needs for normal individuals and that nutrients at these levels are dietary supplements which are foods for special dietary use. No evidence was submitted in the comments to establish a food or nutritional use of vitamin A or vitamin D at higher levels, except for a limited number of persons with poor vitamin D absorption who need up to 1000 IU of this vitamin for nutritional purposes under medical supervision. With that one exception, which is recognized in the revised regulation, intake of vitamins at levels exceeding the upper limits as specified in § 80.1 are therefore appropriate only for therapeutic purposes and thus are properly classed as drugs.

This position is entirely consistent with the Food and Drug Administration's long-standing interpretation and application of the act. See, e.g., Nutrilab, Inc. v. United States, 335 U.S. 365 (1948), in which the Supreme Court upheld the conviction of an individual for marketing "health food products [illegible] "various vitamins, minerals, [illegible]" on the ground that they were misbranded drugs. See also United States v. 3 Cartons * * * "No. 26 Formula GM etc.," 132 F. Supp. 569 (S.D. Calif. 1952).

Alleged differences in [illegible] on their source is also [illegible]

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

Status of Vitamin A and Vitamin D

In the FEDERAL REGISTER of December 14, 1972 (37 FR 26618) the Commissioner of Food and Drugs proposed that preparations containing vitamin A in excess of 10,000 international units (IU) per dosage unit and preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed on prescription. A correction, which did not alter the intent of the proposal, was published in the FEDERAL REGISTER of January 4, 1973 (38 FR 799). Sixty days were allowed for comment.

tentative and final orders promulgating §§ 80.1 and 125.1–125.3. There is no scientific evidence to suggest that there is a difference in the metabolic actions or toxic effects of synthetically produced vitamins as compared with those from natural sources.

2. Several manufacturers and trade associations objected to the proposal on the ground that the proper classification of OTC drug levels of vitamins would be made in the near future by the appropriate OTC drug advisory review panel and that levels established now by the Food and Drug Administration would only be on interim measure. These comments expressed the opinion that deferring action on this proposal would not result in any signficant hazard to the public health.

In the preamble of the proposal the Commissioner stated his reasons for separating vitamin A and vitamin D from the other vitamins at this time and establishing levels above which these vitamins are limited to prescription distribution. The continuing information available to the Commissioner regarding the toxicity of vitamin A and vitamin D and the continuing reports of promotion of large amounts of these vitamins for a variety of purposes makes this action necessary at this time in the public interest.

3. A number of comments from individual consumers and those representing the vitamin industry agreed that vitamin A and vitamin D are toxic in amounts in excess of known requirements, but stated that such levels are much higher than the limitations proposed. Some comments offered a level of 25,000 IU of Vitamin A and 1,000 IU of Vitamin D as providing a sufficient safety margin for known toxicity. Other comments contended that the proposed levels were suitable for children, but higher levels would be more appropriate for adults. A number of comments felt the proposed levels were arbitrary and without scientific merit or support. Several of the comments had made a review and provided their own analysis of the bibliography prepared by the Food and Drug Administration at the time the proposal was published in the FEDERAL REGISTER. Generally, these comments stated that toxicity below 50,000 IU daily for vitamin A was rare and that vitamin D toxicity reports would not support the vitamin D level proposed.

Several other comments recommended lower levels than those proposed. A comment from a physician at a university School of Medicine, Department of Biochemistry, supported the proposal, but stated that 5,000 IU for vitamin A would be a more judicious level. Another comment from the Department of Chemical Pathology, the United Liverpool Hospitals, Liverpool, England, included a reference to a paper written by the respondent regarding self-medication with multivitamin preparations and recommended that 100 IU of vitamin D per dosage unit be the limit for non-prescription marketing.

The Commissioner has carefully reviewed the comments and analysis regarding the medical/scientific justification for establishing the proposed vitamin A and vitamin D limits and finds that such comments do not sufficiently support a revision of the proposed limits. No evidence refuted the toxicity findings on which the proposal was based, and further reports of toxicity continue to accumulate. Based on consultation with the most knowledgeable experts available, the Commissioner finds that the scientific consensus is that the proposed limits are appropriate at this time.

The Commissioner of Food and Drugs will soon publish in the FEDERAL REGISTER a request for submission of all data and information relevant to the safety and effectiveness of vitamins and minerals for OTC drug use, pursuant to the procedures established in 21 CFR 130.301, published in the FEDERAL REGISTER on May 11, 1972 (37 FR 9464). The members of the OTC drug review panel for vitamin-mineral drugs are presently being selected. This panel will have full authority to review and re-evaluate the proper dividing line between OTC and prescription levels of vitamin A and vitamin D, and to recommend to the Commissioner any changes in the regulations promulgated by this order, in its report. Thus, the levels of vitamin A and vitamin D for prescription use in this regulation are established on an interim basis only. These regulations will be revoked upon promulgation of a final OTC drug monograph for vitamin-mineral drugs incorporating final prescription levels for these two vitamins.

4. A number of comments, particularly those from individual consumers, state that it is not logical to require a prescription for dosage levels of vitamins that may be lower than the vitamin content of an average serving of certain foods. A few comments expressed concern that normal diets with or without appropriate vitamin supplementation may lead to toxic conditions.

The Commissioner recognizes that many common foods contain a variety of vitamins and minerals in widely ranging amounts, and that some common foods contain vitamin A in excess of 10,000 IU per serving. It is also recognized, however, that these foods particularly rich in vitamin A are rarely consumed daily in sufficient quantity over the long periods of time required to lead to toxic manifestations. The concern of the Food and Drug Administration is the availability of vitamin A and vitamin D in large dosage units in medicinal forms, i.e. capsules and tablets, particularly in view of the multiplicity of other sources of this vitamin in the daily diet. The convenience of ingestion in this form on a routine basis encourages excessive intake of these vitamins far beyond the average amounts ingested in normal diets of conventional food over extended periods of time. Adequate amounts of vitamin A and vitamin D will continue to be available as dietary supplements and are not being removed from the market place. The margins of safety provided in the levels established by this proposal were developed to take into account the wide range of vitamin content in foods and the dosage levels of vitamin A and vitamin D preparations that are usually implicated in toxic conditions.

5. Comment was received that consumers would be able to ingest as many dosage units as they desired and therefore the proposed limits would have no effect. The Commissioner cannot agree with this concept. Today's consumers are increasingly knowledgeable and are concerned about the health and safety of themselves and their family. The Commissioner believes that most consumers will carefully consider the advisability of taking dosage units in excess of suitable recommended daily dosages. Conscientious consumers will have a basis upon which to make a judgment as to their intake of these vitamins. The fact that a small number of consumers will abuse their health by excessive intakes of drugs, regardless of regulatory and other approaches to curtail such abuse, is no reason to forego a reasonable regulation that will afford appropriate public health protection for the vast majority of the public.

6. The Committee on Nutrition, American Academy of Pediatrics, and several other respondents commented on the special needs for vitamin D in foods for special dietary use in specific medical conditions. Foods designed to provide sound nutrition to individuals with poor vitamin D absorption require higher than normal levels of vitamin D. Such individuals may require dietary intakes up to 1000 IU as part of their overall dietary management.

The Commissioner recognizes that foods represented solely for use under medical supervision to meet nutritional requirements in specific medical conditions have a place in medical care of a select group of individuals who have diagnosed conditions that will benefit from the use of complete foods containing up to 1000 IU of vitamin D. The marketing of such foods is permitted in compliance with § 125.1(h) being published elsewhere in this issue of the FEDERAL REGISTER. The regulation for vitamin D has been revised to allow this limited use of a higher amount of vitamin D without a prescription.

7. Comments received from the Council on Foods and Nutrition, American Medical Association, endorse the proposal and include reference to the possible relationship between excess vitamin D and hypercholesterolemia, in addition to the classic form of vitamin D toxicity. The Council also commented that the proposal fails to mention that there is no recommended dietary allowance for vitamin D for adults, since their needs are considered to be met by ordinary mixed diets and exposure to sunlight. The Council, along with other respondents, raised a question regarding a controlled "overage" to assure compliance with label declarations of the amounts present.

The Food and Drug Administration recognizes that there is no recommended dietary allowance for vitamin D in adults except during pregnancy and lactation and therefore considers vitamin D [illegible]

optional component of dietary supplements of vitamins and minerals for adults and older children (21 CFR 80.1). The Commissioner notes that within good manufacturing practices reasonable overages are permissible in formulating drugs and these are recognized in the specification ranges used in determining whether or not a product meets its labeled potency.

8. In response to the proposal, the Wisconsin Alumni Research Foundation resubmitted comments directed to a proposal regarding vitamin D published in the FEDERAL REGISTER of August 28, 1965 (30 FR 11140). The previous proposal was more restrictive than the present one and contained several provisions not currently being considered. Of significance in this comment was concern by the Wisconsin Alumni Research Foundation that the requirements as proposed in 1965 would have the effect of decreasing the vitamin D intake by the general public to a level below their nutritional needs.

The Commissioner concludes that such a situation is clearly not possible as a result of the current proposal, which is directed only at the use of vitamin D as a drug. As a result of the vitamin D content of milk and other foods, and the availability of vitamin D in dietary supplements, the national food supply provides ample vitamin D.

9. Several manufacturers commented that the effective date of any final order with respect to vitamin A and vitamin D should be the same uniform effective date established for recent food labeling revisions. Such an effective date would permit interstate shipments of existing high potency products through December 31, 1974. Several comments also requested that those vitamin A and vitamin D preparations already in commercial channels be allowed continued marketing until existing supplies are exhausted.

Because of the known toxicity and continuing reports of toxic conditions resulting from large dosages over a period of time, the Commissioner concludes that protracted continuation of manufacture and marketing of preparations that do not meet the requirements of this order is not justified. However, a reasonable period of time to allow for orderly reformulation and relabeling, where necessary, is in the public interest to assure continued availability of vitamin A and vitamin D preparations. Therefore, this order shall become effective for products labeled beginning October 1, 1973. No recall of existing stocks is deemed necessary.

10. One comment from a manufacturer stated that the proposal conflicts with the limits for vitamin A established by the food labeling regulations published in the January 19, 1973 FEDERAL REGISTER (38 FR 2124). The Commissioner finds no conflict between this drug regulation and the food regulations. Those vitamin A preparations within the ranges specified in § 80.1 are considered foods and must be labeled as dietary supplements. Those preparations containing vitamin A in excess of the upper limit of these ranges, but less than the proposed prescription drug level, are OTC drugs. Those preparations containing in excess of 10,000 IU of vitamin A per dosage unit are prescription drugs.

11. Several comments requested that a public hearing be held to consider the issues and objections. A hearing on these matters is not mandatory under section 701(a) of the act. The Commissioner concludes that a hearing is inappropriate at this time and that any further delay in promulgation of these regulations is not in the public interest. A hearing on this issue will be available before both the advisory drug panel and the Commissioner under the OTC drug review procedures.

Having considered the comments received, the Commissioner concludes that the proposed regulations are in the public interest and should be adopted as set forth below.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), Part 3 is amended by adding thereto the following new sections:

§ 3.94 Vitamin A preparations for oral use as drugs.

(a) Vitamin A is an essental nutrient for humans. It is widely recognized that large amounts of vitamin A can cause adverse effects, some of which are serious. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin A is 1500 International Units. (IU) for infants, 2500 IU for children under 4 years of age, 5000 IU for adults and children 4 or more years of age, and 8000 IU for pregnant or lactating women.

(b) In view of the toxicity of excessive consumption of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(c) Preparations containing 10,000 or less IU of vitamin A per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 10,000 IU.

§ 3.95 Vitamin D preparations for oral use as drugs.

(a) Vitamin D is an essential nutrient for humans. It is widely recognized that vitamin D, when ingested daily in large amounts, is toxic. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin D is 400 International Units (IU).

(b) In view of the toxicity of the excessive consumption of vitamin D, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin D toxicity.

(c) Preparations containing 400 or less IU of vitamin D per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 400 IU.

(d) Foods which are represented for use solely under medical supervision to meet nutritional requirements of persons with poor vitamin D absorption may contain vitamin D not in excess of 1000 IU per dosage unit or recommended daily intake.

Effective date. This order shall become effective on October 1, 1973 for products labeled on or after that date.

(Secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a))

Dated: July 25, 1973.

A. M. SCHMITT,
Commissioner of Food and Drugs.

[FR Doc.73-15703 Filed 8-1-73;8:45 am]

The Pharmacopeia of the United States of America

(*The United States Pharmacopeia*)

Eighteenth Revision

By authority of
The United States Pharmacopeial Convention, Inc.,
meeting at Washington, D. C., March 29 and 30, 1960

Prepared by the
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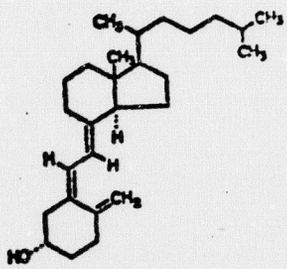
399a

Cholecalciferol

Activated 5,7-Cholestadien-3β-ol
$C_{27}H_{44}O$ 384.65



Description: White, odorless crystals. Is affected by air and by light.
Solubility: Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils.
Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, in the range of 2 μ to 12 μ, exhibits maxima only at the same wavelengths as that of a similar preparation of U. S. P. Cholecalciferol Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of U. S. P. Cholecalciferol Reference Standard, concomitantly measured, and the respective absorptivities at the wavelength of maximum absorbance at about 265 mμ do not differ by more than 3 percent.

C: To a solution of about 0.5 mg. in 5 ml. of chloroform add 0.3 ml. of acetic anhydride and 0.1 ml. of sulfuric acid, and shake vigorously: a bright red color is produced, and it rapidly changes through violet and blue to green.

D: Dissolve 50 mg. of it and 50 mg. of 3,5-dinitrobenzoyl chloride in separate 1-ml. portions of anhydrous pyridine. Mix the solutions, warm on a steam bath for 10 minutes, add 5 ml. of water, filter, and wash the precipitate thoroughly with small portions of cold water. Recrystallize the precipitate twice from acetone, and dry in a vacuum desiccator for 2 hours: the dinitrobenzoyl derivative so obtained melts between 133° and 135°.

Melting range, *Class Ib*, page 935: between 84° and 88°.

Specific rotation, page 936: not less than +105° and not more than +112°, determined in a solution in alcohol containing 50 mg. in each 10 ml. Prepare the solution without delay, using Cholecalciferol from a container opened not longer than 30 minutes, and determine the rotation within 30 minutes after the solution has been prepared.

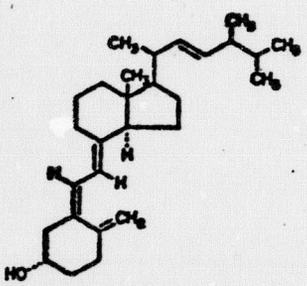
Packaging and storage—Preserve in hermetically sealed containers under nitrogen, in a cool place and protected from light.

CATEGORY: Antirachitic vitamin; also see *Decavitamin Capsules* and *Tablets*.

USUAL DOSE: In rickets—Prophylactic, 10 mcg. (400 U. S. P. Vitamin D Units) once a day.

Therapeutic, 30 mcg. (1200 Units) once a day.

In hypocalcemic tetany—1.25 to 5 mg. (50,000 to 200,000 Units) once a day.



Ergocalciferol

Irradiated Ergosta-5,7,22-trien-3β-ol
$C_{28}H_{44}O$ 396.66

Description: White, odorless crystals. Is affected by air and by light.
Solubility: Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils.
Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, in the range of 2 to 12 μ, exhibits maxima only at the same wavelengths as that of a similar preparation of U. S. P. Ergocalciferol Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of U. S. P. Ergocalciferol Reference Standard, concomitantly measured, and the respective absorptivities at the wavelength of maximum absorbance at about 265 mμ do not differ by more than 3 percent.

C: To a solution of about 0.5 mg. in 5 ml. of chloroform add 0.3 ml. of acetic anhydride and 0.1 ml. of sulfuric acid, and shake vigorously: a bright red color is produced and rapidly changes through violet and blue to green.

D: Dissolve 50 mg. of it and 50 mg. of 3,5-dinitrobenzoyl chloride in separate 1-ml. portions of pyridine. Mix the solutions, warm on a steam bath for 10 minutes, add 5 ml. of water, filter, and wash the precipitate thoroughly with small portions of cold water. Recrystallize the precipitate twice from acetone, and dry in a vacuum desiccator for 2 hours: the dinitrobenzoyl derivative so obtained melts between 147° and 149°.

Melting range, *Class Ib*, page 935: between 115° and 118°.
Specific rotation, page 936: not less than +103° and not more than +106°, determined in a solution in alcohol containing 150 mg. in each 10 ml. Prepare the solution without delay, using Ergocalciferol from a container opened not longer than 30 minutes, and determine the rotation within 30 minutes after the solution has been prepared.
Ergosterol—Dissolve 10 mg. in 2 ml. of 90 percent alcohol, add a solution of 20 mg. of digitonin in 2 ml. of 90 percent alcohol, mix, and allow to stand for 18 hours: no precipitate is formed.
Reducing substances—To 10 ml. of a 1 in 100 solution in dehydrated alcohol add 0.5 ml. of a 1 in 200 solution of blue tetrazolium in dehydrated alcohol. Then add 0.5 ml. of a solution prepared by diluting 1 volume of tetramethylammonium hydroxide T.S. with dehydrated alcohol to make 10 volumes. Allow the mixture to stand for 5 minutes, then add 1 ml. of glacial acetic acid. Prepare a blank by treating 10 ml. of dehydrated alcohol in the same manner. Determine the absorbance of the solution at 525 mμ, with a suitable spectrophotometer, against the blank: the absorbance is not greater than that obtained with a solution containing 0.2 mcg. per ml. of hydroquinone in dehydrated alcohol, similarly treated.
Packaging and storage—Preserve in hermetically sealed containers under nitrogen, in a cool place and protected from light.

Category: Antirachitic vitamin; also see *Decavitamin Capsules* and *Tablets*.
Usual dose: In rickets—Prophylactic, 10 mcg. (400 U. S. P. Vitamin D Units) once a day.
Therapeutic, 30 mcg. (1200 Units) once a day.
In hypocalcemic tetany—1.25 to 5 mg. (50,000 to 200,000 Units) once a day.

Ergocalciferol Capsules

Ergocalciferol Capsules usually consist of an edible vegetable oil solution of ergocalciferol, encapsulated with gelatin. Ergocalciferol Capsules contain not less than 100.0 percent of the labeled amount of $C_{28}H_{44}O$.

Oil solution content of capsules—Weigh accurately 20 Capsules in a tared weighing bottle. Soften the Capsules by exposure to 80 percent relative humidity, then carefully open as by cutting with scissors' tips, without any loss of shell material, and transfer the contents to a suitable container. Remove any oil remaining in the emptied Capsules by washing with small portions of ether, and allow the capsules to dry at room temperature until the odor of ether is no longer perceptible. Weigh the emptied capsules in the same tared bottle in which the full capsules were weighed: the difference represents the weight of the contents of the 20 Capsules.
Assay—Proceed with Ergocalciferol Capsules as directed under *Vitamin D Assay*, page 915.
Packaging and storage—Preserve in tight, light-resistant containers.
Labeling—Label the Capsules to indicate the content of ergocalciferol in mg. and in U. S. P. Vitamin D Units.
Capsules available—Capsules usually available contain the following amount of ergocalciferol: 1.25 mg. (50,000 U. S. P. Vitamin D Units).

Category and Dose: See *Ergocalciferol*.

Ergocalciferol Solution

Ergocalciferol Solution is a solution of ergocalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. It contains, in each g., not less than 250 mcg. (10,000 U. S. P. Vitamin D Units) of $C_{28}H_{44}O$.

Description: Clear liquid having the characteristics of the solvent used in preparing the Solution.
Assay—Proceed with Ergocalciferol Solution as directed under *Vitamin D Assay*, page 915.
Packaging and storage—Preserve in tight, light-resistant containers.
Labeling—Label the Solution to indicate the concentration of ergocalciferol in mg. and in U. S. P. Vitamin D Units.

Category and Dose: See *Ergocalciferol*.

Vitamin A

Vitamin A contains a suitable form of retinol ($C_{20}H_{30}O$; vitamin A alcohol) and possesses vitamin A activity equivalent to not less than 95.0 percent of that declared on the label. It may consist of retinol or esters of retinol formed from edible fatty acids, principally acetic and palmitic acids. It may be diluted with edible oils, or it may be incorporated in solid, edible carriers or excipients, and it may contain suitable antimicrobial agents, dispersants, and antioxidants.

Description: In liquid form, a light-yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. May be nearly odorless or may have a mild fishy odor, but has no rancid odor or taste. Is unstable to air and light.

Solubility: In liquid form, insoluble in water and in glycerin; very soluble in chloroform and in ether; soluble in absolute alcohol and in vegetable oils. In solid form, may be dispersible in water.

Identification for Vitamin A—

A: To 1 ml. of a chloroform solution of it containing the equivalent of approximately 6 mcg. of retinol add 10 ml. of antimony trichloride T.S.: a transient blue color appears at once.

B: Assemble an apparatus for *Thin-layer Chromatography* (see page 796), using chromatographic silica gel as the adsorbant, and a mixture of 4 parts of cyclohexane and 1 part of ether as the solvent system. Prepare a Standard solution by dissolving the contents of 1 capsule of U. S. P. Vitamin A Reference Standard in sufficient chloroform to make 25.0 ml.

If the Vitamin A is in liquid form, dissolve a volume representing approximately 15,000 U. S. P. Units in chloroform to make 10 ml. If the Vitamin A is in solid form, weigh a quantity representing approximately 15,000 U. S. P. Units, place in a separator, add 75 ml. of water, shake vigorously for 1 minute, extract with 10 ml. of chloroform by shaking for 1 minute, and centrifuge to clarify the chloroform extract.

Apply at the starting point of the chromatogram 0.015 ml. of the Standard solution and 0.01 ml. of the solution of Vitamin A. Develop the chromatogram in the chromatographic chamber, lined with filter paper, dipping into the solvent mixture. When the solvent has ascended for a distance of 10 cm., remove the plate, and allow it to dry in air. Spray with antimony trichloride T.S.: the blue spot formed is indicative of the presence of retinol. The approximate R_f values of the predominant spots, corresponding to the different forms of retinol, are: (*alcohol* form) 0.1; (*acetate*) 0.45; and (*palmitate*) 0.7.

Absorbance ratio—The ratio of the corrected observed absorbance [A_{325}] to the absorbance A_{325} determined as directed under *Vitamin A Assay*, page 914, is not less than 0.85.

Assay—Using a suitable quantity of Vitamin A, accurately weighed, proceed as directed under *Vitamin A Assay*, page 914.

Packaging and storage—Preserve in tight containers, preferably under an atmosphere of an inert gas, protected from light.

Labeling—Label it to indicate the form in which the vitamin is present, and to indicate the presence of any antimicrobial agent, dispersant, antioxidant, or other added substance, and to indicate the vitamin A activity in terms of the equivalent amount of retinol, in mg. per g., and in U. S. P. Vitamin A Units.*

CATEGORY: Anti-xerophthalmic vitamin; also see *Decavitamin Capsules* and *Tablets*.

USUAL DOSE: Prophylactic, 1.5 mg. (5000 U. S. P. Vitamin A Units) once a day.

Therapeutic, 7.5 mg. (25,000 Units) once a day.

USUAL DOSE RANGE: Prophylactic, 1.2 to 2.4 mg. (4000 to 8000 Units) daily.

Therapeutic, 7.5 to 60 mg. (25,000 to 200,000 Units) daily.

Vitamin A Capsules

Vitamin A Capsules contain not less than 95.0 percent of the labeled amount of vitamin A.

Weight variation, page 950: meet the requirements for *Capsules*.

Other requirements—The contents of Capsules respond to the *Identification tests* and meet the requirements of the test for *Absorbance ratio* under *Vitamin A*, page 775.

Assay—Using not less than 5 Vitamin A Capsules, proceed as directed under *Vitamin A Assay*, page 914. Calculate the content of retinol ($C_{20}H_{30}O$) in mg. and in U. S. P. Vitamin A Units per Capsule.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—Label Capsules to indicate the form in which the vitamin is present, and to indicate the vitamin A activity in terms of the equivalent amount of retinol in mg. and in U. S. P. Vitamin A Units per Capsule.

Capsules available—Capsules usually available contain the following amounts of vitamin A: 1.5, 7.5, 15, and 30 mg. (5000, 25,000, 50,000, and 100,000 U. S. P. Vitamin A Units).

CATEGORY and DOSE: See *Vitamin A*.

* NOTE—One U. S. P. Vitamin A Unit is the specific biologic activity of 0.3 mcg. of the all-*trans* isomer of retinol.

U. S. P. Reference Standards

Reference Standards are called for in many pharmacopeial assays and tests. Originally introduced for the biological assays of U. S. P. X, the use of reference standards has been extended to the point where they are now required for numerous other pharmacopeial assays as well. Some standards formerly required are still being distributed as a service to pharmacy and medicine for use as needed in unofficial assays.

On occasion, as a possible first step in pharmacopeial standardization, a reference standard or substance is provided as a standardized source of endocrine or enzyme activity in advance of the actual pharmacopeial recognition of a product representing that activity. In these cases, the articles supplied are designated as "substances" if they are heterogeneous in nature and if the prospect of their assuming pharmacopeial status is fairly remote; however, heterogeneous substances may be designated as "reference standards" if they are the counterparts of international standards.

The U. S. P. Reference Standards and U. S. P. Reference Substances are released under the authority of the U. S. P. Board of Trustees upon recommendation by the U. S. P. Reference Standards Committee, which supervises the testing and finally passes upon the suitability of each lot. The critical characteristics of the specimens selected for the standard are usually determined independently in three or more laboratories. At the request of the U. S. P. Reference Standards Committee, the Drug Standards Laboratory (see *Preface*) and the Food and Drug Administration laboratory test almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the nation, both academic and industrial, participate in the testing.

A similar program to provide international standards is maintained by the World Health Organization, an agency of the United Nations. The WHO program is concerned mainly with standards for serums, toxins, vaccines, endocrine extracts, and vitamins. As a rule, an International Standard is no longer provided once the substance responsible for its characteristic activity has been isolated, identified, and

made readily available. A limited number of such compounds are distributed under WHO sponsorship as Authentic Chemical Substances for use in assays and tests of drugs. The U. S. P. Reference Standards Committee collaborates closely with the WHO in order not only to minimize unavoidable differences in the actual units of potency but also in some cases to share in the preparation of a reference standard.

No radioactive U. S. P. Reference Standards are provided, because of the special circumstances surrounding the preparation, storage, and distribution of standardized forms of radioactive substances suitable for use in drug analyses, despite the fact that some are called for in pharmacopeial assays and tests. Reliable standards of some radioactive substances, including chromium 51, cobalt 60, gold 198, iodine 131, and phosphorus 32, are available upon order from commercial sources.

Reference Standards are not available for substances subject to the licensing provisions established for narcotics.

The following U. S. P. Reference Standards are available (the Melting Point Standards are shown in *italics*, where listed individually).

Acetanilid
Acetazolamide
Allopurinol
Amitriptyline Hydrochloride
Amobarbital
Amphotericin B
Ampicillin
Ascorbic Acid
Aspirin
Atropine Sulfate
Benzalkonium Chloride
Benzathine Penicillin G
Gamma Benzene Hexachloride
Benztropine Mesylate
Betazole Hydrochloride
Bishydroxycoumarin
Caffeine
Calcium Disodium Edetate
Calcium Pantothenate
Carbachol
Chlorambucil
Chloramphenicol
Chlordiazepoxide Hydrochloride
Chlorobenzenes
Chloroquine Phosphate
Chlorpheniramine Maleate
Chlorpromazine Hydrochloride
Chlorpropamide
Chlorthalidone
Cholecalciferol[1]
Cholestyramine Resin
Corticotropin
Cortisone Acetate
Cyanocobalamin
Cyclizine Hydrochloride
Cyclophosphamide
Cycloserine
Demecarium Bromide
Deslanoside
Desoxycorticosterone Acetate
Dexamethasone
Dexamethasone Phosphate
Dextroamphetamine Sulfate
Diaminodiphenylsulfone
Dibucaine Hydrochloride
Dichlorphenamide
Diethylstilbestrol
Diethyltoluamide
Digitalis
Digitoxin
Digoxin
Dihydrostreptomycin Sulfate
Dihydrotachysterol
Dioctyl Sodium Sulfosuccinate
Diphenhydramine Hydrochloride
Diphenylhydantoin
Disodium Edetate
Dyclonine Hydrochloride
Edrophonium Chloride
Epinephrine Bitartrate
Equilin
Ergocalciferol[2]
Ergonovine Maleate
Erythromycin
Erythromycin Ethylcarbonate
Erythromycin Gluceptate[3]
Erythromycin Lactobionate
Estradiol Valerate
Estrone
Ethacrynic Acid
Ethinyl Estradiol
Ethionamide
Ethosuximide
Ethoxzolamide
Ethynodiol Diacetate
Evans Blue
Fluorouracil
Fluoxymesterone
Folic Acid
Furosemide
Gallamine Triethiodide
Gentamicin Sulfate
Globin
Glucagon
Chorionic Gonadotropin
Griseofulvin
Guanethidine Sulfate
Hexachlorophene
Histamine Dihydrochloride
Homatropine Hydrobromide
Hydrochlorothiazide
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Sodium Phosphate
Hydrocortisone Sodium Succinate

[1] Formerly called Activated 7-Dehydrocholesterol.

[2] Formerly called Calciferol.

[3] Formerly called Erythromycin Glucoheptonate.

Hydroxychloroquine Sulfate
Hydroxyprogesterone Caproate
Hydroxystilbamidine Isethionate
Idoxuridine
Imipramine Hydrochloride
Indocyanine Green
Insulin
Iodipamide
Iodochlorhydroxyquin
Iothalamic Acid
Isoproterenol Hydrochloride
Kanamycin Sulfate
Levallorphan Tartrate
Levarterenol Bitartrate
Lincomycin Hydrochloride
Liothyronine
Lucanthone Hydrochloride
Mecamylamine Hydrochloride
Meclizine Hydrochloride
Medroxyprogesterone Acetate
Melphalan
Melting Point Standards
Meprobamate
Mercaptopurine
Mestranol
Metaraminol Bitartrate
Methamphetamine Hydrochloride
Methazolamide
Methimazole
Methotrexate Reference Substance
Methyldopa
Methyldopate Hydrochloride
Methylene Blue
Methylergonovine Maleate
Methylphenidate Hydrochloride
Metyrapone
Neomycin Sulfate
Neostigmine Bromide
Neostigmine Methylsulfate
Niacinamide
Nitrofurantoin
Norethindrone
Norethynodrel
Novobiocin
Nystatin
Ouabain
Oxytetracycline
Oxytetracycline Hydrochloride
Phenacetin
Phenacetin
Phenformin Hydrochloride
Phenobarbital
Phenolsulfonphthalein
Phenoxymethyl Penicillin
Phentolamine Mesylate[4]
Phenylephrine Hydrochloride
Physostigmine Salicylate
Phytonadione
Pilocarpine Nitrate
Posterior Pituitary
Negative Control Plastic
Polymyxin B Sulfate
Pralidoxime Chloride
Prednisolone
Prednisolone Acetate
Prednisone
Primidone
Probenecid
Procaine Hydrochloride
Prochlorperazine Maleate
Promethazine Hydrochloride
Proparacaine Hydrochloride
Propoxyphene Hydrochloride
Protamine
Pyrazinamide
Pyridostigmine Bromide
Pyridoxine Hydrochloride
Pyrimethamine
Pyrvinium Pamoate
Quinacrine Hydrochloride
Quinethazone
Quinidine Gluconate
Reserpine
Resorcinol
Riboflavin
Scopolamine Hydrobromide
Secobarbital
Sodium Ampicillin
Sodium Cephalothin
Sodium Cloxacillin
Sodium Colistimethate
Sodium Diatrizoate
Sodium Heparin[5]
Sodium Methicillin
Sodium Nafcillin
Sodium Oxacillin
Sodium Penicillin G
Sodium Sulfobromophthalein
Spironolactone
Streptomycin Sulfate
Sulfadiazine
Sulfamerazine
Sulfamethazine
Sulfanilamide
Sulfanilamide
Sulfapyridine
Sulfisoxazole
Testosterone Cypionate[6]
Testosterone Enanthate
Testosterone Propionate
Tetracaine Hydrochloride
Tetracycline Hydrochloride
Theophylline
Thiabendazole
Thiamine Hydrochloride
Thiopental
Thioridazine Hydrochloride
Thiotepa
Tolazamide
Tolbutamide
Tolnaftate
Triamcinolone
Triamcinolone Acetonide
Triamterene
Trihexyphenidyl Hydrochloride

[4] Formerly called Phentolamine Methanesulfonate.

[5] Formerly called Heparin Sodium.

[6] Formerly called Testosterone Cyclopentylpropionate.

Trimethaphan Camsylate
Tripelennamine Citrate
Tripelennamine Hydrochloride
Tropicamide
Tubocurarine Chloride
Vancomycin Hydrochloride
Vanillin
Vanillin
Vinblastine Sulfate
Vincristine Sulfate
Viomycin Sulfate
Vitamin A
Vitamin D Capsules
Vitamin D Oil
Warfarin
Zinc Bacitracin

Reference Standards and Reference Substances are available on a self-sustaining basis through orders addressed to: U. S. P. Reference Standards, 4630 Montgomery Ave., Bethesda, Md. 20014.

Vitamin A Assay

The following procedure is provided for the determination of vitamin A as an ingredient of Pharmacopeial preparations. It conforms to that which was adopted in 1956 for international use by the International Union of Pure and Applied Chemistry.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to actinic light and to atmospheric oxygen and other oxidizing agents, preferably by the use of non-actinic glassware and an atmosphere of an inert gas.

Special Reagents—

ETHER—Use *Ether*, page 249, freshly redistilled, discarding the first and last 10-percent portions.

Procedure—Accurately weigh, count, or measure a portion of the sample expected to contain the equivalent of not less than 0.15 mg. of retinol but containing not more than 1 g. of fat. If in the form of capsules, tablets, or other solid, reflux the portion taken in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for about 5 minutes longer.

Transfer to a saponification flask, and add 30 ml. of alcohol if the sample is liquid or of 23 ml. of alcohol and 7 ml. of glycerin if the sample is solid, followed by 3 ml. of potassium hydroxide solution (1 in 1). Reflux in an *all-glass* apparatus for 30 minutes. Cool the solution, add 30 ml. of water, and transfer to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract by shaking for 2 minutes with one 150-ml. portion of ether, and, if an emulsion forms, with three additional 25-ml. portions

of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 250-ml. volumetric flask, and add ether to volume.

Evaporate a 25.0-ml. portion of the ether extract to about 5 ml. *Without applying heat and with the aid of a stream of inert gas or vacuum,* continue the evaporation to about 3 ml. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.5 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution at the wavelengths 310 mμ, 325 mμ, and 334 mμ, with a suitable spectrophotometer fitted with matched quartz cells.

WHEN TOCOPHEROL IS PRESENT—Transfer to a saponification flask a suitable sample, accurately measured, or not less than 5 previously crushed Decavitamin Capsules or Decavitamin Tablets. Reflux in an *all-glass* apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (9 in 10) for 30 minutes. Add through the condenser 2.0 g. of hydrous citric acid, washing the walls of the condenser with 10 ml. of water. Cool, and transfer the solution to a conical separator with the aid of 20 ml. of water. Add 2 g. of finely powdered sodium sulfate. Extract with one 150-ml. portion of ether, and, if an emulsion forms, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 250-ml. volumetric flask, and add ether to volume. Transfer a 100.0-ml. aliquot of the resulting ether solution to a conical separator, and wash once with 50 ml. of potassium hydroxide solution (1 in 33), using alcohol, if necessary, to break any emulsion that forms. Wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with three additional 50-ml. portions of water. Transfer the washed ether extract to a 100-ml. volumetric flask, and add ether to volume.

Evaporate a 50.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. *Without applying heat and with the aid of a stream of inert gas or vacuum,* remove the residual ether. Dissolve the residue in 50.0 ml. of isopropyl alcohol.

Hydrogenated portion—Pipet 15 ml. of the isopropyl alcohol solution into a 50-ml. centrifuge tube, add approximately 200 mg. of palladium catalyst, stir with a glass rod, and hydrogenate for 10 minutes in a *Hydrogenator* such as is described in the *Alpha Tocopherol Assay*, page 913, using isopropyl alcohol in the blank tube. Add about 300 mg. of chromatographic siliceous earth, stir with a glass rod, and immediately centrifuge until the solution is clear.

Test a 1-ml. aliquot of the solution by removing the solvent by evaporation, dissolving the residue in 1 ml. of chloroform, and adding 10 ml. of antimony trichloride T.S.: no detectable blue color appears. [NOTE—If a blue color appears, repeat the hydrogenation for a longer time period, or with a new lot of catalyst.]

Into two separate flasks pipet equal volumes of the *Hydrogenated portion* and the untreated isopropyl alcohol solution, respectively, and add sufficient isopropyl alcohol to give an expected concentration of vitamin A equivalent to 3 mcg. to 5 mcg. per ml. Determine the absorbances of the untreated solution against the solution from the *Hydrogenated portion* as a blank, at the wavelengths 310 mμ, 325 mμ, and 334 mμ, with a suitable spectrophotometer fitted with matched quartz cells.

Calculation—Calculate the vitamin A content as follows:

$$\text{Content (in mg.)} = 0.549A_{325}/LC,$$

in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule, or tablet in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than $[A_{325}]/1.030$ and not more than $[A_{325}]/0.970$, where $[A_{325}]$ is the *corrected* absorbance at 325 mμ and is given by the equation $[A_{325}] = 6.815A_{325} - 2.555A_{310} - 4.260A_{334}$, in which A designates the absorbance at the wavelength indicated by the subscript.

Where $[A_{325}]$ has a value less than $A_{325}/1.030$, apply the following equation:

$$\text{Content (in mg.)} = 0.549[A_{325}]/LC,$$

in which the values are as defined herein.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

Vitamin D Assay

The following procedure is provided for the determination of vitamin D as an ingredient of Pharmacopeial preparations.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to air and to

actinic light, preferably by the use of a blanket of inert gas and low-actinic glassware.

Special Reagents and Solutions—

CHROMATOGRAPHIC FULLER'S EARTH—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

SOLVENT HEXANE—Use solvent hexane (see under *Reagents*), redistilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

ETHYLENE DICHLORIDE—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

POTASSIUM HYDROXIDE SOLUTION—Dissolve 500 g. of potassium hydroxide in water to make 1000 ml.

BUTYLATED HYDROXYTOLUENE SOLUTION—Dissolve 10 mg. of butylated hydroxytoluene in 100 ml. of alcohol. Prepare this solution fresh daily.

COLOR REAGENT—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 20-mm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

FIRST COLUMN—Arrange for descending column chromatography a tube of 2.5-cm. (inside) diameter, about 25 cm. long, and constricted to 8-mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

SECOND COLUMN—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

FIRST COLUMN—To about 125 ml. of isooctane contained in a screw-capped, wide-mouth bottle add 25 g. of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 400. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

SECOND COLUMN—Pack the mid-section of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of U. S. P. Ergocalciferol [illegible] Standard, accurately weighed, in sufficient isooctane to give a known concentration of about 250 mcg. per ml. Store in a refrigerator.

On the day of assay, pipet 1 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in and make to volume with *Ethylene Dichloride*.

Sample Preparation—Accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 U. S. P. Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 3000 U. S. P. Units) of vitamin A acetate to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g of the total weight of the sample, but not less than a total of 3.0 ml. Add 10 ml. of *Butylated Hydroxytoluene Solution* and 20 ml. of alcohol. Reflux vigorously on a steam bath for 30 minutes. Cool, and transfer the saponified mixture to a separator, rinsing the saponification flask with three 10-ml. portions of water and three 50-ml. portions of ether, adding the rinse to the separator. Add about [illegible] sodium sulfate decahydrate to the separator

and extract by shaking for 2 minutes. If an emulsion forms, extract with three 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously with additional 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, add ether to volume, and mix. Transfer the entire sample or an accurately measured aliquot containing about 250 mcg. to a tall-form, 400-ml. beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, then decant the solution into a second 400-ml. beaker. Rinse the sodium sulfate with three 25-ml. portions of ether, adding each rinse to the main portion. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with three 10-ml. portions of ether, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation*.

Procedure—

FIRST COLUMN CHROMATOGRAPHY—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column*, pipet 2 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 100 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40° or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane*.

SECOND COLUMN CHROMATOGRAPHY—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column*. Rinse the evaporation flask with a total of 10 ml. of *Solvent Hexane* in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about −125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

ASSAY PREPARATION—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml. volumetric flask, and make to volume with *Ethylene Dichloride* to obtain the *Assay Preparation*.

COLOR DEVELOPMENT—Into each of three suitable, matched colorimeter tubes of about 20-mm. (inside) diameter, and designated *1*, *2*, and *3*, respectively, pipet 1 ml. of the *Assay Preparation*. Into tube *1* pipet 1 ml. of the *Standard Preparation*, into tube *2*, 1 ml. of *Ethylene Dichloride*, and into tube *3*, 1 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add quickly, and preferably from an automatic pipet, 5.0 ml. of *Color Reagent*, and mix. After 45 seconds, accurately timed, following the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes *2* and *3* at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(Cs/C)(Au/As)$, in which Cs is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, Au has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and As has the value of $A^1_{500} - A^3_{500}$ determined on the solution from the *Standard Preparation*.

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VITAMIN A ASSAY

Complete the assay promptly and exercise care throughout the procedure to avoid undue exposure to oxidizing agents, to actinic light, and to other conditions that destroy vitamin A. The use of nonactinic glassware is advantageous in avoiding destruction by light.

Isopropyl alcohol—Use *Isopropyl Alcohol*, distil, if necessary, to meet the following requirements for spectral purity: when measured in a 1-cm. cell against distilled water it shows an absorbance not greater than 0.05 at 300 mμ and not greater than 0.01 between 320 mμ and 350 mμ.

Ether—Use *Ether*, freshly distilled, discarding the first and last 10 percent portions, or *Ether*, anesthetic grade, from a freshly opened container.

Saponification—Transfer to a saponification flask an amount of the sample, accurately measured and expected to contain not less than the equivalent of 150 mcg. of vitamin A, but not more than 1 g. of fat. Reflux in an *all-glass* **apparatus with 30 ml. of alcohol and 3 ml. of potassium hydroxide solution (1 in 2) for 30 minutes. Cool the solution, add 30 ml. of water, and transfer the resulting solution to a conical separator. Add 2 g. of finely powdered sodium sulfate. Extract, by shaking for 2 minutes, with one 150-ml. portion of ether, or, if an emulsion occurs, with three additional 25-ml. portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml. of water. Repeat the washing more vigorously until the last washing** gives no color with phenolphthalein T.S. Transfer the washed ether extract to a 250-ml. volumetric flask, and dilute to volume with ether.

Procedure—Evaporate a 25.0-ml. aliquot of the ether solution of the unsaponifiable extract to about 5 ml. Without the application of heat, reduce the volume to about 3 ml. in a stream of inert gas or under reduced pressure. Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent of 3 to 5 mcg. of vitamin A per ml. or such that it will give an absorbance in the range 0.4 to 0.8 at 325 mμ. Determine the absorbances of the resulting solution in 1-cm. cells, at 310 mμ, 325 mμ, and 334 mμ with a suitable spectrophotometer, using isopropyl alcohol as the blank.

Calculation—Calculate the vitamin A content as follows: Vitamin A content (in mg.) = 0.549 × (A_{325}/LC), in which A_{325} is the observed absorbance at 325 mμ, L is the length, in cm., of the absorption cell, and C is the amount of sample expressed as g., capsule or tablet, in each 100 ml. of the final isopropyl alcohol solution, provided that A_{325} has a value not less than A_{325}(cor.)/1.030 and not more than A_{325} (cor.)/0.970, where A_{325}(cor.) = $0.815A_{325} - 2.555A_{310} - 4.200A_{334}$, in which A designates the absorbance at the wavelengths indicated by the subscripts. Where A_{325}(cor.) has a value less than A_{325}/1.030 apply the following formula: Vitamin A content, in mg., = $0.549[A_{325}/LC]$. Each mg. of vitamin A (alcohol)

represents 3333 USP Units of vitamin A.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

VITAMIN D ASSAY

Biological Method

The biological assay of vitamin D comprises the recording and interpretation of observations on groups of rats maintained on specified dietary regimens throughout specified periods of their lives whereby the biological response to the preparation under assay is compared with the response to USP Vitamin D Reference Standard.

Preliminary Period—Throughout the preliminary period in the life of a rat, which is not longer than 30 days and extends from birth to the first day of the depletion period, maintain litters of rats under the immediate supervision of, or according to the directions of, the individual responsible for the assay. During the preliminary period, use a dietary regimen which provides for normal development but is limited in its content of vitamin D, so that when placed upon the *Rachitogenic Diet* in the depletion period the rats develop rickets. At the end of the preliminary period, reject any rat which weighs less than 44 g. or more than 60 g., or which shows evidence of injury, disease, or anatomical abnormality.

Depletion Period—Through the depletion period, which extends from the end of the preliminary period to the first day of the assay period, provide each rat *ad libitum* with the *Rachitogenic Diet* and water and allow access to no other food or dietary supplement.

Rachitogenic Diet—The rachitogenic diet consists of a uniform mixture of the following ingredients in the proportions shown:

	Parts by Weight
Whole Yellow Corn, ground	76
Ground Wheat Gluten	20
Calcium Carbonate	3
Sodium Chloride	1

When a chemical analysis of the entire ration shows a Ca:P ratio of less than 4:1 or more than 5:1, the proportion of calcium carbonate may be varied to bring the adjusted ratio to a uniform level within this range.

Assigning Rats to Groups for the Assay Period—Consider a litter suitable for the assay period when individual rats in the litter show evidence of rickets such as enlarged joints and a distinctive wobbly, rachitic gait, provided that the depletion period is not less than 19 or more than 25 days. The presence of rickets may be established also from the width of the rachitic metaphysis upon X-ray examination or by applying the line test (described below) to a leg bone of one member of each litter.

Record the weight of each rat and assign it to a group, in which each rat will be fed a specified dose of the reference standard or of an assay sample that is under examination for its vitamin D potency. For each assay sample provide one or more assay groups and at least two standard groups. The two standard groups may be used for the concurrent assay of more than one assay sample. Within an interval not exceeding 30 days, complete the assignment of rats to groups according to a design which divides litters among the groups, to achieve a complete balance.

For complete balance, whereby each litter is represented equally in every group, use seven or more litters containing at least as many depleted rats as there are groups. From a given litter, assign one rat, selected at random, to each group on the same day. If a litter contains twice as many rats as there are groups, assign a second series of rats similarly. The last one or two litters to be assigned may be allotted to groups so that at the start of the assay period the average body weight of any completed groups will not differ by more than 8 g. from that of any other group.

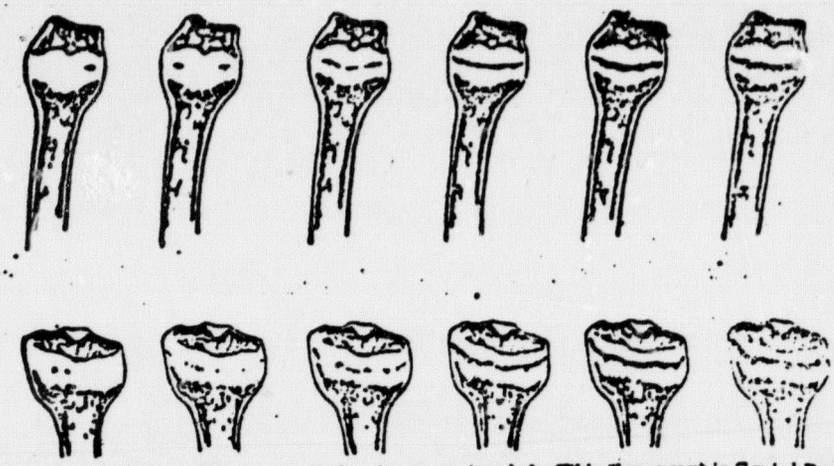
Assay Doses—Select two dosage levels of the USP Vitamin D Reference Standard, spaced so that the ratio of the larger to the smaller dose is not less than 1.5 or more than 2.5. Select one or two dosage levels based upon a single assumed potency for each sample. The dosage levels of the sample are equivalent to those of the standard or to a mid-level equal to the square root of the product of the two dosage levels of the standard.

Select dosage levels such that, when fed to rachitic rats, they are expected to produce degrees of calcification within the range specified under the test of data acceptability. Before feeding, the reference standard and/or sample may be diluted with cottonseed oil, provided that not more than 0.2 ml. is fed on any one day. Store the oil solutions in well-closed bottles, protected from light, at a temperature not exceeding 10°, and use within 5 weeks.

Assign one group of rats to each dosage level of the standard and of the one or more samples.

Assay Period—During the assay period, which extends from the end of the depletion period for a fixed interval of 7 to 10 days, cage each rat individually and provide it *ad libitum* with the *Rachitogenic Diet* and water. Supply a rachitogenic diet prepared from the same lots of ingredients to all rats. On the first and on the third (or fourth) day of the assay period, feed each rat one-half of its total assigned dose.

Throughout the assay period, maintain as uniform environmental conditions as possible for all rats and exclude exposure to



Representative Sections Showing the Radius (upper row) and the Tibia (lower row) in Graded Degrees of Healing in Rachitic Rats within the Useful Range of the Dosage-Response Relationship of the Vitamin D Assay

antirachitic radiations. At the end of a fixed period of 7 to 10 days, weigh and kill each rat. From those rats which do not weigh less at the end than at the start of the assay period and which have consumed each assigned dose within 24 hours of the time it was fed, dissect out one or more leg bones for examination by the *Line Test*.

Line Test—Remove the proximal end of a tibia or the distal end of a radius and clean it of adhering tissue, in any one assay using the same bone from all animals. With a clean, sharp blade cut a median, longitudinal section through the juncture of the epiphysis and diaphysis at the same place on each bone. Rinse both sections in purified water, immerse immediately in silver nitrate solution (1 in 50) for 1 minute, and rinse again in purified water. Expose the cut surface of bone, in water, to daylight or another source of actinic light until the calcified areas develop a clearly defined stain without marked discoloration of the uncalcified areas. The staining procedure may be modified to differentiate more clearly between calcified and uncalcified areas.

Score the degree of calcification of the rachitic metaphysis in each rat, according to a scale which allows the average response to be plotted as a straight line against the logarithm of the dose. The figure presented illustrates the range of the degree of calcification best suited for assay purposes.

Acceptability—Observations are acceptable for use in calculation of the potency only from those groups in which two-thirds or more but not less than 7 rats show calcification at least as great as the lowest level and not greater than the highest level illustrated in the figure. If the average score of the standard group on the high dosage level is not greater than the average score of the standard group on the low dosage level, discard the results and repeat the assay. If an assay sample is represented solely by assay groups which are not acceptable for measuring vitamin D potency and in each of which the average score is less than the average score of the standard group on the low dosage level or more than the average score of the standard group on the high dosage level, the assayed content of vitamin D is comparatively less than that represented by the low dose or more than that represented by the high dose of the Reference Standard.

Calculation—Tabulate the scores (*y*), listing each litter in a separate row with treatment groups in columns. Omit any groups which do not meet the test for *Acceptability*. Equalize the number of observations in the acceptable groups by disregarding the results on all litters not equally represented in the groups or by other suitable means (see *Design and Analysis of Biological Assays*, USP XVIII). Total the *f* scores for each of the treatment groups, where *f* is the number of litters, and designate each total as *T* with subscripts 1 and 2 for the low and high dosage levels, respectively. Compute the slope *b* from the sums of T_1, *i.e.*, ΣT_1, and of T_2, *i.e.*, ΣT_2, for the standard and sample, provided the latter is represented at both dosage levels as $b = (\Sigma T_2 - \Sigma T_1)/fh'$, where *i* is the logarithm of the ratio of the high dose to the low dose and is the same for each preparation, and h' is the number of preparations represented by two dosage levels and included in the calculation of the value of *b*.

Compute the logarithm of the relative potency of each sample under assay as log (relative potency) = $M' = (\bar{y}_u - \bar{y}_s)/ih'T_s/2\Sigma T_s$, where each mean score, $\bar{y}_u$ for the assay sample and $\bar{y}_s$ for the Reference

Standard, is the average of the individual scores for an intermediate dosage level or of the two means for the high and the low dosage levels and where $T_s = \Sigma T_2 - \Sigma T_1$ and T_s is defined in USP XVIII. Convert each observed M' to its antilogarithm to obtain the relative potency of the sample. Multiply the relative potency by the assumed potency of the assay oil in Units per g., adopted at the start of the assay, to obtain its assayed content of vitamin D in USP Units per g.

Chemical Method

The following procedure is provided for the determination of vitamin D as an ingredient of official preparations containing other active constituents.

Special Reagents and Solutions—

Chromatographic Fuller's Earth—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

Solvent Hexane—Use reagent solvent hexane (see USP XVIII), distilling if necessary so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm. cell at 300 mμ, with a suitable spectrophotometer, against air as the blank: the absorbance is not more than 0.070.

Ethylene Dichloride—Purify by passage through a column of granular (20 to 200 mesh) silica gel.

Potassium Hydroxide Solution—Dissolve 780 g. of potassium hydroxide in water to make 1000 ml.

Cottonseed Oil—Use cottonseed oil USP that meets the following additional requirement: Saponify 10 g. of the oil as directed in this chapter under *Sample Preparation*, beginning with "then add a volume of *Potassium Hydroxide Solution*," and dissolve the unsaponifiable residue in 10 ml. of *Solvent Hexane*.

In a separate container place 0.4 ml. of ferric chloride solution (1 in 1000) and 12 ml. of a 1 in 6000 solution of 2,2'-bipyridine in dehydrated alcohol, mix, and 5 minutes later read the absorbance in a 1-cm. cell at 520 mμ, with a suitable spectrophotometer, using dehydrated alcohol as the blank. Then add 0.2 ml. of the solvent hexane solution of the unsaponifiable residue, and after 5 minutes read the absorbance. The difference between the first and the second absorbances is not less than 0.125.

Color Reagent—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g. bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml. of *Ethylene Dichloride*. Add about 2 g. of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered, container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml., and mix: the absorbance of the solution, measured in a 2-cm. cell at 500 mμ, with a suitable spectrophotometer, against *Ethylene Dichloride*, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml. of acetyl chloride and 400 ml. of *Ethylene Dichloride*.

Mix 45 ml. of *Solution A* and 5 ml. of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

First Column—Arrange for descending column chromatography (see page 780) a tube of 2.5 cm. (inside) diameter, about 25 cm. long, and constricted to 8 mm. diameter for a distance of 5 cm. at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

Second Column—Select a tube that is made up of three sections: (1) a flared top section, 18 mm. in (inside) diameter and approximately 14 cm. long, (2) a middle section, 6 mm. in (inside) diameter and approximately 25 cm. long, and (3) a tapered, constricted lower exit tube approximately 5 cm. long. Insert a small plug of glass wool in the upper 1-cm. portion of the constricted section.

Chromatographic Columns—

First Column—To about 125 ml. of isooctane contained in a screw-cap, wide-mouth bottle add 25 g. of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous mixing, 10 ml. of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm. disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml. of isooctane.

Second Column—Pack the midsection of the tube with 3 g. of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about −125 mm. of mercury).

Standard Preparation—Dissolve about 25 mg. of USP Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to make 100.0 ml. Store in a refrigerator.

On the day of assay, pipet 1.0 ml. of the standard solution into a 50-ml. volumetric flask, remove the solvent with a stream of nitrogen, and dissolve the residue in, and dilute to volume with, *Ethylene Dichloride*.

Sample Preparation—Unless otherwise

directed, accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 mcg. but preferably about 250 mcg. of ergocalciferol (10,000 USP Units). If little or no vitamin A is present in the sample, add about 1.5 mg. (the equivalent of 5000 USP Units) of vitamin A to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml. of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add 2 ml. of *Cottonseed Oil*, then add a volume of *Potassium Hydroxide Solution* representing 2.5 ml. for each g. of the total weight of the sample plus cottonseed oil, but not less than 15 ml. Add 50 ml. of alcohol. Reflux vigorously on a steam bath for 20 minutes, or for 30 minutes for samples weighing more than 5 g. If oil globules are evident, indicating incomplete saponification, add 5 ml. of *Potassium Hydroxide Solution* (but not exceeding a total of 100 ml.), and heat again. Cool, and transfer the saponified mixture to a 500-ml. separator, rinsing the saponification flask with a total of 50 ml. of water and adding each rinse to the separator. Add about 4.5 g. of sodium sulfate decahydrate and 150 ml. of *Solvent Hexane*. Shake vigorously for 2 minutes. When the aqueous layer has separated, transfer it to a second separator. Extract with two 50-ml. portions of *Solvent Hexane*, combine the extracts, and discard the aqueous solution.

Wash the combined solvent hexane extracts with 50-ml. portions of water until the last portion shows no pink color on the addition of phenolphthalein T.S. Allow the washed extract to stand for 5 minutes, discard any water that separates, and transfer the extract to a 300-ml. tall form beaker containing about 5 g. of anhydrous sodium sulfate. Stir for 2 minutes, and decant the solution into a 500-ml., tall-form beaker. Rinse the sodium sulfate with four 25-ml. portions of *Solvent Hexane*, combining the rinsings with the original extract. Reduce the total volume to about 30 ml. by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with four 5-ml. portions of *Solvent Hexane*, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml. volumetric flask, and dilute with *Solvent Hexane* to volume to obtain the *Sample Preparation*.

Procedure—

First Column Chromatography—Just as the 2 ml. of isooctane disappears into the surface of the prepared *First Column*, pipet 2.0 ml. of the *Sample Preparation* onto the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml. portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml. until 150 ml. has been added. If necessary, adjust the flow rate to between 3 and 6 ml. per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml. of eluate, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm. from the bottom of the column. (The ultraviolet lamp should provide some radiation in the 300-mμ region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the solvent hexane completely under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml. of *Solvent Hexane*.

Second Column Chromatography—Add the solvent hexane solution obtained as directed under *First Column Chromatography* onto the *Second Column*. Rinse the evaporation flask with a total of 10 ml. of solvent hexane in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml. of the solvent hexane remains above the surface of the column, add 75 ml. of benzene, and elute with the aid of gentle suction (about 125 mm. of mercury), collecting the eluate. Evaporate the benzene under vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

Assay Preparation—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml. volumetric flask, and dilute to volume with *Ethylene Dichloride* to obtain the *Assay Preparation*.

Color Development—Into each of three suitable, matched colorimeter tubes of about 2-cm. diameter, and designated *1*, *2*, and *3*, respectively, pipet 1.0 ml. of the *Assay Preparation*. Into tube *1* pipet 1.0 ml. of the *Standard Preparation*, into tube *2*, 1.0 ml. of *Ethylene Dichloride*, and into tube *3*, 1.0 ml. of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add [illegible] preferably from an automatic pipet [illegible]

ml. of *Color Reagent*, and mix. Exactly 45 seconds after the addition of the color reagent, determine the absorbances of the three solutions at 500 mμ, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes 2 and 3 at 550 mμ, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in mcg., of vitamin D in the portion of the sample taken by the formula $(C_S/C) \times (A_U/A_S)$, in which C_S is the concentration of vitamin D in mcg. per ml. of the *Standard Preparation*, C is the concentration of the sample (as g., capsules, tablets, etc.) in each ml. of the final solution, A_U has the value of $(A^2_{500} - A^3_{500}) - 0.67(A^2_{550} - A^3_{550})$ determined from the absorbances observed on the solution from the *Assay Preparation*, and A_S has the value of $A^1_{500} - A^2_{500}$ determined on the solution from the *Standard Preparation*.

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...metals, page 619—To the residue obtained in the test ...*ition* add 4 ml of dilute hydrochloric acid ... cover, digest on a steam bath for 15 minutes, uncover, ... evaporate on a steam bath to dryness. Moisten ... with 1 drop of hydrochloric acid, add 10 ml of hot ..., and digest for 2 minutes. Add ammonia TS dropwise ... solution is just alkaline to litmus paper, and dilute ... water to 25 ml: the limit is 0.001%.

Assay—Dissolve about 200 mg of Chlorthalidone, accurately weighed, in 50 ml of acetone, and titrate in an atmosphere of nitrogen with 0.1 *N* tetrabutylammonium hydroxide dissolved in a mixture of 9 volumes of benzene and 1 volume of methanol, using a buret having a carbon-dioxide absorption trap. Determine the end-point potentiometrically, using a glass-calomel electrode system (with a salt bridge of 0.01 *N* tetrabutylammonium bromide in methanol). Perform a blank determination, and make any necessary correction. Calculate the quantity, in mg, of $C_{14}H_{11}ClN_2O_4S$ in the portion of Chlorthalidone taken by the formula $33.8S[M_S - (M_A S/A)]$, in which M_S is the number of ml of the 0.1 *N* tetrabutylammonium hydroxide mixture consumed in the *Assay*, M_A is the number of ml of 0.1 *N* sodium hydroxide consumed in the test for *Acidity*, S is the weight, in mg, of Chlorthalidone taken for this assay, and A is the weight, in mg, of Chlorthalidone taken for the *Acidity* test.

Chlorthalidone Tablets

Category: Diuretic.

Usual dose: 100 mg once a day.

Usual dose range: 50 to 200 mg daily or every other day.

Usual pediatric dose: 2 mg per kg of body weight or 60 mg per square meter of body surface, three times a week.

Tablets available—Tablets usually available contain the following amounts of chlorthalidone: 50 and 100 mg.

Dispensing information—

Note: Potassium sources (such as orange or tomato juice, bananas, citrus fruits, melons) usually may be included in the diet to prevent electrolyte imbalance.

Advice: Notify physician if loss of appetite, nausea, lethargy, muscle weakness, or other signs of electrolyte imbalance occur. Drug will cause increased urination.

» Chlorthalidone Tablets contain not less than 92.0 percent and not more than 108.0 percent of the labeled amount of $C_{14}H_{11}ClN_2O_4S$.

Packaging and storage—Preserve in well-closed containers.

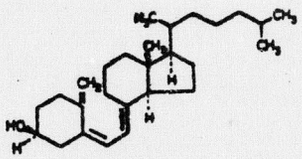
Identification—Digest a quantity of powdered Tablets, equivalent to about 100 mg of chlorthalidone, with 10 ml of methanol on a steam bath for about 5 minutes. Filter the solution into a 50-ml beaker add 20 ml of water, and boil on the steam bath for about 5 minutes, passing a gentle current of air above the solution to remove the methanol. Cool to room temperature, filter, and dry the crystals at 105° for 1 hour: the crystals so obtained melt between 215° and 222°, with decomposition, and respond to *Identification test C* under *Chlorthalidone*, page 90.

Disintegration, page 650: 15 minutes.

Content uniformity, page 648: meet the requirements for *Tablets*.

Assay—Weigh and finely powder not less than 20 Chlorthalidone Tablets. Weigh accurately a portion of the powder, equivalent to about 400 mg of chlorthalidone, and transfer to a glass-stoppered, 100-ml conical flask. Add 40 ml of acetone and a few glass beads, and boil on a steam bath for about 5 minutes. Cool, insert the stopper in the flask, then stir, preferably with a magnetic stirrer, for 15 minutes, and filter through a medium-porosity, sintered-glass filter into a 100-ml volumetric flask. Rinse the flask and the filter funnel with two 10-ml portions of hot acetone, collecting the rinsings in the volumetric flask. Evaporate on a steam bath to dryness, add 40 ml of methanol, warm gently on the steam bath, with constant agitation, for about 3 minutes, and shake by mechanical means for 30 minutes. Add methanol to volume, mix, and clarify, if necessary, by centrifuging in a glass-stoppered vessel. Pipet 25 ml of the clear solution into a 100-ml volumetric flask, dilute with methanol to volume, then pipet 10 ml of the resulting solution into a 100-ml volumetric flask, add 2 ml of dilute hydrochloric acid (1 in 6), and add methanol to volume. Dissolve an accurately weighed quantity of USP Chlorthalidone Reference Standard in a 1 in 50 solution of dilute hydrochloric acid (1 in 6) in methanol, and dilute quantitatively and stepwise with the same solvent to obtain a Standard solution having a known concentration of about 100 µg per ml. Concomitantly determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 275 nm, with a suitable spectrophotometer, using a 1 in 50 solution of dilute hydrochloric acid (1 in 6) in methanol as the blank. Calculate the quantity, in mg, of $C_{14}H_{11}ClN_2O_4S$ in the portion of the Tablets taken by the formula $4C(A_U/A_S)$, in which C is the concentration, in µg per ml, of USP Chlorthalidone Reference Standard in the Standard solution, and A_U and A_S are the absorbances of the solution from the Tablets and the Standard solution, respectively.

Cholecalciferol



$C_{27}H_{44}O$ 384.64

9,10-Secocholesta-5,7,10(19)-trien-3-ol, (3β)-.

Cholecalciferol [67-97-0].

Category: See *Decavitamin Capsules* and *Tablets*.

Description: White, odorless crystals. Is affected by air and by light.

Solubility: Insoluble in water; soluble in alcohol, in chloroform, and in fatty oils.

Packaging and storage—Preserve in hermetically sealed containers under nitrogen, in a cool place and protected from light.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, in the range of 2 µm to 12 µm, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cholecalciferol Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Cholecalciferol Reference Standard, concomitantly measured, and the respective absorptivities at the wavelength of maximum absorbance at about 265 nm do not differ by more than 3%.

C: To a solution of about 0.5 mg in 3 ml of chloroform add 0.3 ml of acetic anhydride and 0.1 ml of sulfuric acid, and shake vigorously: a bright red color is produced, and it rapidly changes through violet and blue to green.

D: Prepare without heating, and handle without delay, a 1 in 100 solution of squalane in chloroform containing 50 mg of cholecalciferol per ml, and prepare a Standard solution of USP Cholecalciferol Reference Standard in the same solvent and of the same concentration. Spot 10 µl of the test solution and 10 µl of the Standard solution on a line parallel to and about 2.5 cm from the bottom edge of a thin-layer chromato-

tographic plate (see page 637) coated with a 0.25-mm layer of chromatographic silica gel mixture. Place the plate in a developing chamber containing and equilibrated with a mixture of equal volumes of cyclohexane and diethyl ether. Develop the chromatogram until the solvent front has moved about 15 cm above the line of application. Perform the development and subsequent operations in the dark. Remove the plate, allow the solvent to evaporate, and spray with a 1 in 50 solution of acetyl chloride in antimony trichloride TS: the chromatogram obtained with the test solution shows a yellowish orange area (cholecalciferol) having the same R_f value as the area of the Standard solution, and may show below the cholecalciferol area a violet area attributed to 7-dehydrocholesterol.

Melting range, *Class Ib*, page 651: between 84° and 88°.

Specific rotation, page 652: between +105° and +112°, determined in a solution in alcohol containing 50 mg in each 10 ml: Prepare the solution without delay, using Cholecalciferol from a container opened not longer than 30 minutes, and determine the rotation within 30 minutes after the solution has been prepared.

Cholera Vaccine

Cholera Vaccine

Category: Active immunizing agent.

Usual dose: Intramuscular or subcutaneous, 0.5 ml, then 1 ml four weeks later, and a 0.5-ml reinforcing dose repeated every six months if necessary.

Usual pediatric dose:

Under five years of age: 0.1 ml, then 0.3 ml four weeks later, and a 0.1-ml reinforcing dose repeated every six months if necessary.

Five to ten years of age: 0.3 ml, then 0.5 ml four weeks later, and a 0.3-ml reinforcing dose repeated every six months if necessary.

Over ten years of age: See *Usual dose*.

Sizes available—It is usually available standardized to contain 8000 million organisms per ml, in 1.5- or 20-ml vials.

Description: Practically water-clear liquid to milky suspension, nearly odorless or having a faint odor due to the antimicrobial agent.

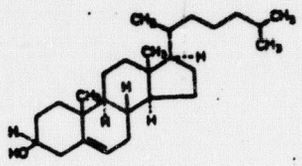
» Cholera Vaccine is a sterile suspension, in isotonic sodium chloride solution or other suitable diluent, of killed cholera vibrios (*Vibrio choleræ*). It is prepared from equal portions of suspensions of cholera vibrios of the Inaba and Ogawa strains. Its labeled potency is based on the U. S. Standard Vaccines of the federal Food and Drug Administration for the respective serotypes. It contains a suitable antimicrobial agent. Its production and distribution are subject to federal regulations (see *Biologics*, page 675).

Packaging and storage—Preserve at a temperature between 2° and 8°.

Expiration date—Its expiration date is not later than 18 months after date of issue from manufacturer's cold storage (5°, 1 year).

Other requirements—It complies with the requirements under *Biologics*, page 675, and with the safety, sterility, potency, and other requirements of the federal FDA.

Cholesterol



$C_{27}H_{46}O$ 386.67
Cholest-5-en-3-ol, (3β)-.
Cholest-5-en-3β-ol [57-88-5].

Category: Pharmaceutic aid (emulsifying agent); see also *Hydrophilic Petrolatum*.

Description: White or faintly yellow, almost odorless, pearly leaflets or granules. Acquires a yellow to pale tan color on prolonged exposure to light.

Solubility: Insoluble in water; soluble in acetone, in chloroform, in dioxane, in ether, in ethyl acetate, in solvent hexane, and in vegetable oils; sparingly soluble in dehydrated alcohol; slightly (and slowly) soluble in alcohol.

» Cholesterol is a steroid alcohol used as an emulsifying agent.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Identification—

A: To a solution of 10 mg in 1 ml of chloroform add 1 ml of sulfuric acid: the chloroform acquires a blood-red color and the sulfuric acid shows a green fluorescence.

B: Dissolve about 5 mg in 2 ml of chloroform, add 1 ml of acetic anhydride, and follow with 1 drop of sulfuric acid: a pink color is produced, and it rapidly changes to red, then to blue, and finally to a brilliant green.

Melting range, page 651: between 147° and 150°.

Specific rotation, page 652: between −34° and −38°, determined in a solution in dioxane containing 200 mg in each 10 ml.

Loss on drying, page 651—Dry it in vacuum at 60° for 4 hours: it loses not more than 0.3% of its weight.

Residue on ignition, page 620: not more than 0.1%.

Acidity—Dissolve 1.0 g in 10 ml of ether in a small flask, add 10.0 ml of 0.1 *N* sodium hydroxide, and shake for about 1 minute. Heat gently to expel the ether, and then boil for 5 minutes. Cool, dilute with 10 ml of water, add phenolphthalein TS, and titrate with 0.1 *N* sulfuric acid until the pink color just disappears. Perform a blank determination (see *Residual Titrations*, page 629). The difference between the number of ml of 0.1 *N* sulfuric acid consumed in the blank and the number of ml consumed in the test with the Cholesterol is not more than 0.3 ml.

Solubility in alcohol—Dissolve 500 mg in 50 ml of warm alcohol in a stoppered flask or cylinder, and allow to stand at room temperature for 2 hours: no deposit or turbidity is formed.

Cholestyramine Resin

Cholestyramine.
Cholestyramine [11041-12-6].

Category: See *Cholestyramine for Oral Suspension*.

Description: White to buff-colored, hygroscopic, fine powder. Is odorless or has not more than a slight amine-like odor.

Solubility: Insoluble in water, in alcohol, in benzene, in chloroform, and in ether.

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the same wavelengths as that of a similar solution of USP Dapsone Reference Standard, concomitantly measured.

Melting range, page 651: between 173° and 181°.

Loss on drying, page 651—Dry it at 105° for 3 hours: it loses not more than 1.5% of its weight.

Residue on ignition, page 620: not more than 0.1%.

Selenium, page 621: 0.003%, a 100-mg sample, mixed with 100 mg of magnesium oxide, being used.

Assay—Weigh accurately about 250 mg of Dapsone, and proceed as directed under *Nitrite Titration*, page 626. Each ml of 0.1 *M* sodium nitrite is equivalent to 12.42 mg of $C_{12}H_{12}N_2O_2S$.

Dapsone Tablets

Category: Antibacterial (leprostatic); dermatitis herpetiformis suppressant.

Usual dose:

Leprostatic—25 mg two times a week for one month, then increased by 25 mg per dose at monthly intervals to a maximum of 100 mg four times a week.

Dermatitis herpetiformis suppressant—100 to 200 mg once a day.

Usual dose range:

Dermatitis herpetiformis suppressant—50 to 400 mg daily.

Usual pediatric dose:

Leprostatic—6 to 12.5 mg two times a week for one month, then increased by 6 to 12.5 mg per dose at monthly intervals to a maximum of 50 mg four times a week.

Tablets available—Tablets usually available contain the following amounts of dapsone: 25 and 100 mg.

Dispensing information—

Advice: Notify physician if skin rash, itching, fever, sore throat, unusual bleeding or bruising, nausea, vomiting, diarrhea, headache, or malaise occurs. Take with a full glass of water.

» Dapsone Tablets contain not less than 92.5 percent and not more than 107.5 percent of the labeled amount of $C_{12}H_{12}N_2O_2S$.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Identification—Triturate a quantity of finely powdered Tablets, equivalent to about 100 mg of dapsone, with 50 ml of methanol, and filter. Dilute a portion of the filtrate with methanol to make approximately a 1 in 200,000 solution: this solution responds to the *Identification test* under *Dapsone*, page 118.

Disintegration, page 650: 30 minutes.

Weight variation, page 670: meet the requirements for *Tablets*.

Assay—Weigh and finely powder not less than 20 Dapsone Tablets. Weigh accurately a portion of the powder, equivalent to about 250 mg of dapsone, and proceed as directed for *Procedure* under *Nitrite Titration*, page 626, beginning with "transfer to a suitable open vessel." Each ml of 0.1 *M* sodium nitrite is equivalent to 12.42 mg of $C_{12}H_{12}N_2O_2S$.

Decavitamin Capsules

Category: Combination vitamins.

Usual dose: 1 capsule daily.

» Decavitamin Capsules contain, in each Capsule, not less than the labeled amounts of retinol, in the form of vitamin A; vitamin D from natural sources or as ergocalciferol, or cholecalciferol, or the products obtained by the activation of either ergosterol or 7-dehydrocholesterol; ascorbic acid ($C_6H_8O_6$) or its equivalent as sodium ascorbate; calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$) or its equivalent as racemic calcium pantothenate or its equivalent as D-panthenol or racemic panthenol; cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$); folic acid ($C_{19}H_{19}N_7O_6$); niacinamide ($C_6H_6N_2O$); pyridoxine hydrochloride ($C_8H_{11}NO_3.HCl$); riboflavin ($C_{17}H_{20}N_4O_6$); thiamine hydrochloride ($C_{12}H_{17}ClN_4OS.HCl$) or its equivalent as thiamine mononitrate; and a suitable form of alpha tocopherol.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—The label indicates the forms of vitamins A and D, thiamine, and tocopherol, respectively, that are present, and indicates the quantity of each vitamin present in the Capsules.

Weight variation, page 670: meet the requirements for *Capsules*.

Assay for vitamin A—Using not less than 5 Decavitamin Capsules, proceed as directed under *Vitamin A Assay*, page 632. Calculate the content of retinol ($C_{20}H_{30}O$) in mg and in USP Units per Capsule.

Assay for vitamin D—Using not less than 20 Decavitamin Capsules, proceed as directed under *Vitamin D Assay*, page 633. Calculate the content of vitamin D in terms of the equivalent, in μg, of ergocalciferol and in USP Units per Capsule.

Assay for ascorbic acid—Add not less than 10 Decavitamin Capsules to 75 ml of metaphosphoric-acetic acids TS, and heat rapidly to a temperature not exceeding 90°, with continuous swirling until complete disintegration occurs. Transfer the suspension to a glass-stoppered, 500-ml volumetric flask containing 125 ml of metaphosphoric-acetic acids TS, and immediately cool rapidly to room temperature. Transfer any remaining residue by rinsing with four or five 10-ml portions of the extracting solution, and dilute with water to volume. Transfer, if necessary, any solid fatty material to the wall of the flask above the calibration line, using a dry glass rod so as not to affect the volume of the water solution. After thorough mixing, the fatty solids may be removed. Use an aliquot that will consume not less than 20 ml of standard dichlorophenol-indophenol solution, and titrate with standard dichlorophenol-indophenol solution (see *Volumetric Solutions*) until a pink color persists for not less than 5 seconds. Correct for the volume of the dichlorophenol-indophenol solution consumed by a mixture of 5.5 ml of the metaphosphoric-acetic acids TS and 15 ml of water.

From the ascorbic acid equivalent of the standard dichlorophenol-indophenol solution, calculate the content of $C_6H_8O_6$ in each Capsule.

Assay for calcium pantothenate—Place a counted number of Decavitamin Capsules, equivalent to about 25 mg of dextrorotatory calcium pantothenate, in a 500-ml flask, add 20 ml of a 1 in 10 solution of polysorbate 80 in alcohol, 10 ml of chloroform, 20 ml of a solution containing, in each 1000 ml, 440 mg of anhydrous dibasic sodium phosphate and 95 mg of anhydrous citric acid, and 20 ml of water, and heat at about 50°, with frequent swirling of the contents until the Capsules are dissolved or thoroughly disintegrated. The solution or disintegration of the Capsules may be accomplished also by the use of a mechanical shaker or suitable blender. When the Capsules are dissolved, cool if necessary, dilute with water to 1000.0 ml, and mix. Make further dilutions with water to a concentration of 0.01 to 0.04 μg of dextrorotatory calcium pantothenate per ml, and proceed as directed under *Calcium Pantothenate Assay*, page 618.

Assay for cyanocobalamin—Using not less than 5 Decavitamin Capsules, proceed as directed under *Vitamin B_{12} Activity*

Assay, page 613. Calculate the content, in µg, of cyanocobalamin present in each Capsule.

Assay for folic acid—Cut open or disperse a counted number of Decavitamin Capsules, equivalent to about 1 mg of folic acid, into a volume of dibasic potassium phosphate solution (1 in 33) representing not less than 10 ml for each g of Capsules taken. Heat the mixture to a temperature not exceeding 60°, with swirling, until dispersion is complete, cool, and adjust the volume so that each ml of the mixture represents between 0.005 and 0.01 mg of folic acid. Allow the solid matter to settle, and clarify a portion of the supernatant liquid by filtering or centrifuging. Dilute a measured portion of the filtrate with the phosphate solution to obtain the *Assay Preparation*, each ml of which represents about 5 µg of folic acid, and proceed as directed under *Folic Acid Assay*, page 624.

Assay for niacinamide—Cut open, without appreciable loss, a counted number of Decavitamin Capsules, equivalent to about 100 mg of niacinamide. Add 10 ml of chloroform, stir well, and transfer the mixture to a 500-ml volumetric flask with the aid of about 100 ml of hot water. Add 10 ml of hydrochloric acid, and heat on a steam bath, with frequent swirling, until the Capsules are dissolved or thoroughly disintegrated. Cool, add water to volume, mix, and filter a suitable portion of the solution through a dry filter into a dry flask, rejecting the first 15 to 20 ml of filtrate. Transfer an accurately measured volume of the subsequent filtrate, equivalent to about 2 to 3 mg of niacinamide, to a 500-ml volumetric flask, add 10 ml of water and 10 ml of hydrochloric acid, and evaporate with the aid of heat to about 2 ml. Add 25 ml of water, and neutralize with sodium hydroxide solution (1 in 10). Cool, add water to volume, and mix. Using this solution as the *Assay preparation*, proceed as directed in the *Assay* under *Niacinamide Injection*, page 340, hydrolyzing the standard by the same procedure as for the sample. Calculate the quantity, in mg, of $C_6H_6N_2O$ in each ml of the portion, V, of filtrate taken by the formula $(2.5/V)(Au/As)$, and express the result in terms of the quantity, in mg, of niacinamide present in each Capsule.

Assay for pyridoxine hydrochloride—

Ammonia–ammonium chloride buffer—Dissolve 16 g of ammonium chloride in 70 ml of water, add 16 ml of stronger ammonia water, dilute with water to 100 ml, mix, and filter.

Chlorimide solution—Dissolve 40 mg of 2,6-dichloroquinonechlorimide in 100 ml of isopropyl alcohol. Store the solution in a refrigerator, and use within one month. Do not use the solution if it has become pink.

Standard stock solution—Accurately weigh 25 mg of USP Pyridoxine Hydrochloride Reference Standard, previously dried in vacuum over silica gel for 4 hours, dissolve in 250.0 ml of dilute hydrochloric acid (1 in 100), and mix. Keep the solution in amber bottles in a cool place.

Standard preparation—Dilute 10.0 ml of *Standard stock solution* with water to 100.0 ml, and mix. Prepare this solution daily as needed.

Assay preparation—Cut open, without appreciable loss, a counted number of Decavitamin Capsules, equivalent to about 10 mg of pyridoxine hydrochloride, and transfer with the aid of water to a conical flask. Add 5 ml of hydrochloric acid, dilute with water to about 250 ml, and heat on a steam bath until disintegration is complete. Cool, transfer to a 500-ml volumetric flask, dilute with water to volume, mix, and filter or centrifuge. Transfer 25.0 ml of the solution to a 50-ml volumetric flask, add 10 ml of sodium hydroxide TS, mix, then add 200 mg of manganese dioxide, and heat on a steam bath for 30 minutes with frequent agitation. Cool, dilute with water to volume, mix, filter through a dry filter into a dry flask, rejecting the first 10 ml of filtrate, and centrifuge.

Procedure—

(a) Pipet 5 ml of the clear *Assay preparation* into a flask, add 25.0 ml of isopropyl alcohol, and mix. Pipet 5 ml of the isopropyl alcohol dilution into a glass-stoppered, 25-ml graduated cylinder or test tube, and add in succession, mixing after each addition, 1.0 ml of *Ammonia–ammonium chloride buffer*, 1.0 ml of sodium acetate solution (1 in 5), and 1.0 ml of water. Cool to about 25°, then add 1.0 ml of *Chlorimide solution*, shake vigorously for 10 seconds, immediately and 60 seconds, accurately timed, after the addition of the *Chlorimide solution*, determine the absorbance at the wavelength of maximum absorbance at about 650 nm, with a suitable spectrophotometer, using water as the blank. [NOTE—Make the reading promptly to avoid errors due to fading of the color.]

(b) Repeat procedure (a), but substitute 1.0 ml of boric acid solution (1 in 20) for the 1.0 ml of water. Designate the absorbance as Av'.

(c) Repeat procedure (a), but substitute 5.0 ml of the *Standard preparation* for the 5.0 ml of the *Assay preparation*. Designate the absorbance as As.

(d) Repeat procedure (c), but substitute 1.0 ml of boric acid solution (1 in 20) for the 1.0 ml of water. Designate the absorbance as As'.

Calculate the quantity, in mg, of $C_8H_{11}NO_2$.HCl in each Capsule by the formula $(10/N)(Av - Av')/(As - As')$, in which N is the number of Capsules taken.

Assays for riboflavin and thiamine hydrochloride or mononitrate—Using not less than 10 Decavitamin Capsules, proceed as directed in the *Assay* under *Riboflavin Tablets*, page 442, and under *Thiamine Assay*, page 629. If thiamine is present as the mononitrate, conduct the assay as for the hydrochloride, but use the conversion factor given in the *Assay* under *Thiamine Mononitrate*, page 503.

Assay for α-tocopherol—Using not less than 5 Decavitamin Capsules, proceed as directed under *Alpha Tocopherol Assay*, page 631. Calculate the content of alpha tocopherol in mg per Capsule.

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Decavitamin Tablets

Category: Combination vitamins.

Usual dose: 1 tablet daily.

» Decavitamin Tablets contain, in each Tablet, not less than the labeled amounts of retinol, in the form of vitamin A; vitamin D from natural sources or as ergocalciferol, or cholecalciferol, or the products obtained by the activation of either ergosterol or 7-dehydrocholesterol; ascorbic acid ($C_6H_8O_6$) or its equivalent as sodium ascorbate; calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$) or its equivalent as racemic calcium pantothenate or its equivalent as D-panthenol or racemic panthenol; cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$); folic acid ($C_{19}H_{19}N_7O_6$); niacinamide ($C_6H_6N_2O$); pyridoxine hydrochloride ($C_8H_{11}NO_2$.HCl); riboflavin ($C_{17}H_{20}N_4O_6$); thiamine hydrochloride ($C_{12}H_{17}ClN_4O_5$.HCl) or its equivalent as thiamine mononitrate; and a suitable form of alpha tocopherol.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Labeling—The label indicates the forms of vitamins A and D, thiamine, and tocopherol, respectively, that are present, and indicates the quantity of each vitamin present in the Tablets.

Disintegration, page 650: 1 hour.

Weight variation, page 670: meet the requirements for *Tablets*.

Assay for vitamin A—Using not less than 5 Decavitamin Tablets, proceed as directed under *Vitamin A Assay*, page 632, grinding the sample in 20 ml of the alcohol used in the saponification step, then transferring the resulting mixture to the saponification flask with the aid of the remaining alcohol required. Calculate the content of retinol ($C_{30}H_{50}O$) in mg and in USP Units per Tablet.

Assay for vitamin D—Weigh not less than 20 Decavitamin Tablets, and reduce them as nearly as possible to a homogeneous mass. Without delay, weigh accurately a portion of the [illegible] as directed in the [illegible] page 633. Calculate the content of vitamin D in equivalent, in µg, of ergocalciferol and in USP Units per Tablet.

Assay for ascorbic acid—Grind not less than 10 Decavitamin Tablets in a mortar, in sufficient metaphosphoric-acetic acids

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TS to make a paste. Transfer the paste to a 500-ml volumetric flask with the aid of 225 ml of metaphosphoric-acetic acids TS, dilute with water to volume, and proceed as directed in the *Assay for ascorbic acid* under *Decavitamin Capsules*, page 119, beginning with "Use an aliquot."

Assay for calcium pantothenate—Using a counted number of Decavitamin Tablets, equivalent to about 25 mg of dextrorotatory calcium pantothenate, proceed as directed in the *Assay for calcium pantothenate* under *Decavitamin Capsules*, page 119.

Assay for cyanocobalamin—Using not less than 5 Decavitamin Tablets, proceed as directed under *Vitamin B_{12} Activity Assay*, page 613. Calculate the content, in µg, of cyanocobalamin present in each Tablet.

Assay for folic acid—Using a counted number of Decavitamin Tablets, proceed as directed in the *Assay for folic acid* under *Decavitamin Capsules*, page 119.

Assay for niacinamide—Proceed as directed in the *Assay for niacinamide* under *Decavitamin Capsules*, page 119, crushing the Tablets well before the treatment with chloroform. Express the result in terms of the quantity, in mg, of niacinamide present in each Tablet.

Assay for pyridoxine hydrochloride—Use the reagents listed in, and prepare the *Standard preparation* as directed in, the *Assay for pyridoxine hydrochloride* under *Decavitamin Capsules*, page 119.

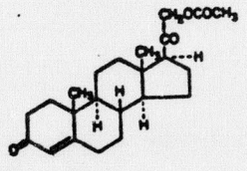
Assay preparation—Finely powder a counted number of Decavitamin Tablets, equivalent to about 10 mg of pyridoxine hydrochloride. Transfer the powder, with the aid of water, to a 500-ml volumetric flask, and proceed as directed in the *Assay for pyridoxine hydrochloride* under *Decavitamin Capsules*, page 119, beginning with "Add 5 ml of hydrochloric acid," under *Assay preparation*. Calculate the quantity, in mg, of $C_8H_{11}NO_3.HCl$ in each Tablet by the formula $(10/N)(Au - Au')/(As - As')$, in which N is the number of Tablets taken.

Assays for riboflavin and thiamine hydrochloride or mononitrate—Using not less than 10 Decavitamin Tablets, proceed as directed in the *Assay* under *Riboflavin Tablets*, page 442, and under *Thiamine Assay*, page 629. If thiamine is present as the mononitrate, conduct the assay as for the hydrochloride, but use the conversion factor given in the *Assay* under *Thiamine Mononitrate*, page 503.

Assay for α-tocopherol—Using not less than 5 Decavitamin Tablets, proceed as directed under *Alpha Tocopherol Assay*, page 631. Calculate the content of alpha tocopherol in mg per Tablet.

Dental Paste, Triamcinolone Acetonide *page 516*

Desoxycorticosterone Acetate



$C_{23}H_{32}O_4$ 372.50
Pregn-4-ene-3,20-dione, 21-(acetyloxy)-.
11-Deoxycorticosterone acetate [56-47-3].

Category: See *Desoxycorticosterone Acetate Injection*.

Description: White or creamy white, crystalline powder. Is odorless and is stable in air.

Solubility: Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in dioxane; slightly soluble in vegetable oils.

» Desoxycorticosterone Acetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{23}H_{32}O_4$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried in vacuum over silica gel for 4 hours, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Desoxycorticosterone Acetate Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Desoxycorticosterone Acetate Reference Standard, concomitantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 240 nm, do not differ by more than 3%.

Melting range, page 651: between 155° and 161°.

Specific rotation, page 652: between +168° and +176°, determined in a solution in dioxane containing 100 mg in each 10 ml.

Loss on drying, page 651—Dry it in vacuum over silica gel for 4 hours: it loses not more than 0.5% of its weight.

Assay—

Standard preparation—Prepare as directed for *Standard Preparation* under *Blue Tetrazolium Assay for Steroids*, page 622, using USP Desoxycorticosterone Acetate Reference Standard.

Assay preparation—Weigh accurately about 100 mg of Desoxycorticosterone Acetate, dissolve in sufficient alcohol to make 200.0 ml, and mix. Pipet 5 ml of this solution into a 250-ml volumetric flask, add alcohol to volume, and mix. Pipet 20 ml of the resulting solution into a glass-stoppered, 50-ml conical flask.

Procedure—Proceed as directed for *Procedure* under *Blue Tetrazolium Assay for Steroids*, page 622. Calculate the quantity, in mg, of $C_{23}H_{32}O_4$ in the Desoxycorticosterone Acetate taken by the formula $100(Au/As)$.

Desoxycorticosterone Acetate Injection

Category: Adrenocortical steroid (salt regulating).

Usual dose: Intramuscular or subcutaneous, 1 to 6 mg once a day.

Usual dose range: 1 to 10 mg daily.

Usual pediatric dose: Intramuscular, 1 to 5 mg once a day, or 1.5 to 2 mg per square meter of body surface, once a day.

Injection available—Injection usually available contains the following amount of desoxycorticosterone acetate: 5 mg per ml.

» Desoxycorticosterone Acetate Injection is a sterile solution of desoxycorticosterone acetate in vegetable oil. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_{23}H_{32}O_4$.

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type III glass, protected from light.

Identification—Evaporate 25 ml of the *Assay preparation* from the *Assay* on a steam bath just to dryness, and dissolve the residue in 1 ml of chloroform. Using this as the test solution, proceed as directed under *Thin-layer Chromatographic Identification Test*, page 617.

Other requirements—It meets the requirements under *Injections*, page 582.

sterile, buffered, aqueous solution of epinephrine bitartrate. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of $C_9H_{13}NO_3.C_4H_6O_6$. It contains a suitable antibacterial agent and may contain suitable preservatives.

Note—Do not use the Ophthalmic Solution if it is brown or contains a precipitate.

Packaging and storage—Preserve in small, well-filled, tight, light-resistant containers.

pH, page 653: between 3.0 and 3.8.

Other requirements—It responds to the *Identification test* under *Epinephrine Nasal Solution*, page 170. It meets also the requirements under *Sterility Tests*, page 592.

Assay—Pipet a volume of Epinephrine Bitartrate Ophthalmic Solution, equivalent to 55 to 60 mg of epinephrine bitartrate, into a 125-ml separator, add water to make 10 ml, and extract the solution with two 10-ml portions of carbon tetrachloride. Then proceed as directed in the *Assay* under *Epinephrine Nasal Solution*, page 170, beginning with "Rinse the stopper and mouth of the separator," but use for the acetylation 1.05 g of sodium bicarbonate and 0.50 ml of acetic anhydride, and extract the acetylated product with six 15-ml portions of chloroform instead of the 25-ml portions therein specified. Calculate the quantity, in mg, of $C_9H_{13}NO_3.C_4H_6O_6$ in the portion of Ophthalmic Solution taken by the formula $1.0775W(0.5 + 0.5R/93)$, in which W is the weight, in mg, and R is the specific rotation (in degrees, without regard to the sign), of the isolated triacetylepinephrine.

Epinephrine Bitartrate for Ophthalmic Solution

Category: Adrenergic (ophthalmic).

For external use: Topically to the conjunctiva, the equivalent of 0.05 ml of a 1.1 percent solution of epinephrine two times a day to once every three days.

Size available—It is usually available containing the equivalent of the following amount of epinephrine: 55 mg.

Dispensing information—

Label: For the eye. Beyond-use date.

Note: Explain administration technique.

Advice: Protect the solution from light and do not use it if it is brown or contains a precipitate. Occasional stinging or burning of the eye may occur after application.

Description: White to off-white solid.

» Epinephrine Bitartrate for Ophthalmic Solution is a sterile, dry mixture of epinephrine bitartrate and suitable antioxidants, prepared by freeze-drying. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_9H_{13}NO_3.C_4H_6O_6$.

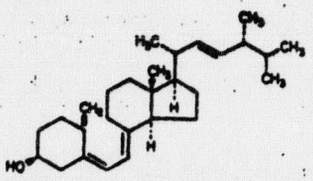
Packaging and storage—Preserve in *Containers for Sterile Solids* as described under *Injections*, page 582.

Completeness of solution, page 642—A 100-mg portion dissolves in 5 ml of water to yield a clear solution.

Other requirements—A solution of it responds to the *Identification test* under *Epinephrine Nasal Solution*, page 170, and meets the requirements of the *Assay* under *Epinephrine Bitartrate Ophthalmic Solution*, page 171. It meets also the requirements under *Sterility Tests*, page 592, and *Content Uniformity—Sterile Solids*, page 648.

429a

Ergocalciferol



$C_{28}H_{44}O$ 396.65

9,10-Secoergosta-5,7,10(19),22-tetraen-3-ol,(3β)-.

Ergocalciferol [*50-14-6*].

Category: See *Ergocalciferol Capsules; Ergocalciferol Solution; Ergocalciferol Tablets;* see also *Decavitamin Capsules* and *Decavitamin Tablets.*

Description: White, odorless crystals. Is affected by air and by light.

Solubility: Insoluble in water; soluble in alcohol, in chloroform, in ether, and in fatty oils.

» Ergocalciferol is 9,10-secoergosta-5,7,10(19),22-tetra-en-3β-ol.

Packaging and storage—Preserve in hermetically sealed containers under nitrogen, in a cool place and protected from light.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, in the range of 2 to 12 μm, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Ergocalciferol Reference Standard.

B: The ultraviolet absorption spectrum of a 1 in 100,000 solution in alcohol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Ergocalciferol Reference Standard, concomitantly measured, and the respective absorptivities at the wavelength of maximum absorbance at about 265 nm do not differ by more than 3%.

C: To a solution of about 0.5 mg in 5 ml of chloroform add 0.3 ml of acetic anhydride and 0.1 ml of sulfuric acid, and shake vigorously: a bright red color is produced and rapidly changes through violet and blue to green.

D: Prepare without heating, and handle without delay, a 1 in 100 solution of squalane in chloroform containing 50 mg of Ergocalciferol per ml, and prepare a Standard solution of USP Ergocalciferol Reference Standard in the same solvent and of the same concentration. Prepare a 1 in 100 solution of squalane in chloroform containing 100 μg of USP Ergosterol Reference Standard per ml. Spot 10 μl of the test solution, 10 μl of the Standard solution, and 10 μl of the ergosterol solution on a line parallel to and about 2.5 cm from the bottom edge of a thin-layer chromatographic plate (see page 637) coated with a 0.25-mm layer of chromatographic silica gel mixture. Place the plate in a developing chamber containing, and equilibrated with, a mixture of equal volumes of cyclohexane and ether. Develop the chromatogram until the solvent front has moved about 15 cm above the line of application. Perform the development and subsequent operations in the dark. Remove the plate, allow the solvent to evaporate, and spray with a 1 in 50 solution of acetyl chloride in antimony trichloride TS. The chromatogram obtained with the test solution shows a yellowish orange area (ergocalciferol) having the same R_f value as the area of the Standard solution of ergocalciferol and may show a violet area below the ergocalciferol area. The color of the violet area is not more intense than that of the violet area in the chromatogram obtained with the solution of ergosterol.

Melting range, *Class Ib,* page 651: between 115° and 118°.

Specific rotation, page 652: between +103° and +106°, determined in a solution in alcohol containing 150 mg in each 10 ml. Prepare the solution without delay, using Ergocalciferol from a container opened not longer than 30 minutes, and determine the rotation within 30 minutes after the solution has been prepared.

Reducing substances—To 10 ml of a 1 in 100 solution in dehydrated alcohol add 0.5 ml of a 1 in 200 solution of blue tetrazolium in dehydrated alcohol. Then add 0.5 ml of a solution prepared by diluting 1 volume of tetramethylammonium hydroxide TS with dehydrated alcohol to make 10 volumes.

Allow the mixture to stand for 5 minutes, accurately timed, then add 1 ml of glacial acetic acid. Prepare a blank by treating 10 ml of dehydrated alcohol in the same manner. Determine the absorbance of the solution at 525 nm, with a suitable spectrophotometer, against the blank: the absorbance is not greater than that obtained with a solution containing 0.2 µg per ml of hydroquinone in dehydrated alcohol, similarly treated.

Ergocalciferol Capsules

Category: Vitamin D (antirachitic).

Usual dose:

Rickets—*Prophylactic*—See *Ergocalciferol Solution*.

Therapeutic—Deficiency rickets—See *Ergocalciferol Solution*. Refractory rickets—1.25 to 25 mg (50,000 to 1,000,000 Units) once a day.

Hypocalcemic tetany—1.25 to 10 mg (50,000 to 400,000 Units) once a day.

Capsules available—Capsules usually available contain the following amounts of ergocalciferol: 625 µg (25,000 Units); 1.25 mg (50,000 Units).

Dispensing information—

Advice: Notify physician if signs of hypervitaminosis D (anorexia, nausea, vomiting, weakness, weight loss, diarrhea, vague aches, stiffness, drowsiness) occur.

» Ergocalciferol Capsules usually consist of an edible vegetable oil solution of ergocalciferol, encapsulated with gelatin. Ergocalciferol Capsules contain not less than 100.0 percent and not more than 120.0 percent of the labeled amount of $C_{28}H_{44}O$.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—Label the Capsules to indicate the content of ergocalciferol in mg and in USP Vitamin D Units.

Weight variation, page 670: meet the requirements for *Capsules*.

Assay—Proceed with Ergocalciferol Capsules as directed under *Vitamin D Assay*, page 633.

Ergocalciferol Solution

Category: Vitamin D (antirachitic).

Usual dose:

Rickets—*Prophylactic*—10 µg (400 USP Vitamin D Units) once a day.

Therapeutic—Deficiency rickets—300 µg to 1.25 mg (12,000 to 50,000 Units) once a day. Refractory rickets, 1.25 to 25 mg (50,000 to 1,000,000 Units) once a day.

Hypocalcemic tetany—1.25 to 10 mg (50,000 to 400,000 Units) once a day.

Solution available—Solution usually available contains the following amount of ergocalciferol: 250 µg (10,000 Units) per g.

Dispensing information—

Advice: Notify physician if signs of hypervitaminosis D (anorexia, nausea, vomiting, weakness, weight loss, diarrhea, vague aches, stiffness, drowsiness) occur.

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Description: Clear liquid having the characteristics of the solvent used in preparing the Solution.

» Ergocalciferol Solution is a solution of ergocalciferol in an edible vegetable oil, in polysorbate 80, or in propylene glycol. It contains, in each g, not less than 250 µg (10,000 USP Vitamin D Units) of $C_{28}H_{44}O$.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—Label the Solution to indicate the concentration of ergocalciferol in mg and in USP Vitamin D Units.

Assay—Proceed with Ergocalciferol Solution as directed under *Vitamin D Assay*, page 633.

Ergocalciferol Tablets

Category: Vitamin D (antirachitic).

Usual dose:

Rickets—*Prophylactic*—See *Ergocalciferol Solution*.

Therapeutic—Deficiency rickets—See *Ergocalciferol Solution*. Refractory rickets—1.25 to 25 mg (50,000 to 1,000,000 Units) once a day.

Hypocalcemic tetany—1.25 to 10 mg (50,000 to 400,000 Units) once a day.

Tablets available—Tablets usually available contain the following amount of ergocalciferol: 1.25 mg (50,000 Units).

Dispensing information—

Advice: Notify physician if signs of hypervitaminosis D (anorexia, nausea, vomiting, weakness, weight loss, diarrhea, vague aches, stiffness, drowsiness) occur.

» Ergocalciferol Tablets contain not less than 100.0 percent and not more than 120.0 percent of the labeled amount of $C_{28}H_{44}O$.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—Label the Tablets to indicate the content of ergocalciferol in mg and in USP Vitamin D Units.

Identification—

A: Evaporate under a stream of nitrogen to dryness 1 ml of the filtrate obtained in *Identification test B*, and dissolve the residue in 50 ml of alcohol: the ultraviolet absorption spectrum of the solution exhibits maxima and minima at the same wavelengths as that of a similar preparation of USP Ergocalciferol Reference Standard, concomitantly measured.

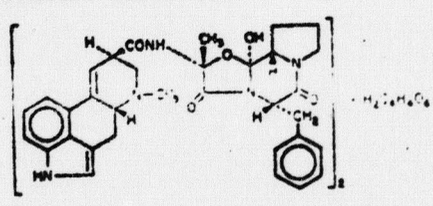
B: Triturate a quantity of powdered Tablets, equivalent to about 5 mg of ergocalciferol, with 10 ml of chloroform, and filter into a small flask: the filtrate so obtained responds to *Identification test C* under *Ergocalciferol*, page 172.

Disintegration, page 650: 30 minutes.

Weight variation, page 670: meet the requirements for *Tablets*.

Assay—Proceed with Ergocalciferol Tablets as directed under *Vitamin D Assay*, page 633.

Ergotamine Tartrate



Packaging and storage—Preserve in tight containers.

Other requirements—It complies with the identification, pyrogen, safety, sterility, pH, moisture content, histamine, potency, and other requirements of the federal FDA concerning viomycin sulfate.

Sterile Viomycin Sulfate

Category: Antibacterial (tuberculostatic).

Usual dose: Intramuscular, the equivalent of 1 gram of viomycin two times a day, twice weekly.

Usual dose range: 4 to a maximum of 14 grams weekly.

Usual pediatric dose: Use in children is not recommended unless crucial to therapy. The equivalent of 20 mg per kg of body weight or 600 mg of viomycin per square meter of body surface two times a day, twice weekly.

Sizes available—It is usually available containing the equivalent of the following amounts of viomycin: 1 and 5 g.

Description and Solubility: See *Viomycin Sulfate*.

• Sterile Viomycin Sulfate is viomycin sulfate suitable for parenteral use. It contains the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amount of viomycin. It conforms to the regulations of the federal Food and Drug Administration concerning antibiotic drugs (see *Antibiotics*, page 673).

Packaging and storage—Preserve in *Containers for Sterile Solids* as described under *Injections*, page 382. The constituted solution may be stored up to 1 week in a refrigerator.

Other requirements—It conforms to the definition under *Viomycin Sulfate*, page 536. It complies with the identification, pyrogen, safety, sterility, pH, moisture content, histamine, potency, and other requirements of the federal FDA concerning sterile viomycin sulfate.

Vitamin A

Category: See *Vitamin A Capsules*.

Description: In liquid form, a light-yellow to red oil that may solidify upon refrigeration. In solid form, has the appearance of any diluent that has been added. May be nearly odorless or may have a mild fishy odor, but has no rancid odor or taste. Is unstable to air and light.

Solubility: In liquid form, insoluble in water and in glycerin; very soluble in chloroform and in ether; soluble in absolute alcohol and in vegetable oils. In solid form, may be dispersible in water.

• Vitamin A contains a suitable form of retinol ($C_{20}H_{30}O$; vitamin A alcohol) and possesses vitamin A activity equivalent to not less than 95.0 percent of that declared on the label. It may consist of retinol or esters of retinol formed from edible fatty acids, principally acetic and palmitic acids. It may be diluted with edible oils, or it may be incorporated in solid, edible carriers or excipients, and it may contain suitable antimicrobial agents, dispersants, and antioxidants.

Packaging and storage—Preserve in tight containers, preferably under an atmosphere of an inert gas, protected from light.

Labeling—Label it to indicate the form in which the vitamin is present, and to indicate the presence of any antimicrobial agent, dispersant, antioxidant, or other added substance, and to indicate the vitamin A activity in terms of the equivalent amount of retinol, in mg per g, and in USP Vitamin A Units.†

Identification for vitamin A—

A: To 1 ml of a chloroform solution of it containing the equivalent of approximately 6 µg of retinol add 10 ml of antimony trichloride TS: a transient blue color appears at once.

B: Assemble an apparatus for *Thin-layer Chromatography* (see page 637), using chromatographic silica gel as the adsorbant, and a mixture of 4 parts of cyclohexane and 1 part of ether as the solvent system. Prepare a Standard solution by dissolving the contents of 1 capsule of USP Vitamin A Reference Standard in chloroform to make 25.0 ml.

If the Vitamin A is in liquid form, dissolve a volume representing approximately 15,000 USP Units in chloroform to make 10 ml. If the Vitamin A is in solid form, weigh a quantity representing approximately 15,000 USP Units, place in a separator, add 75 ml of water, shake vigorously for 1 minute, extract with 10 ml of chloroform by shaking for 1 minute, and centrifuge to clarify the chloroform extract.

Apply at the starting point of the chromatogram 0.015 ml of the Standard solution and 0.01 ml of the solution of Vitamin A. Develop the chromatogram in the chromatographic chamber, lined with filter paper, dipping into the solvent mixture. When the solvent has ascended for a distance of 10 cm, remove the plate, and allow it to dry in air. Spray with antimony trichloride TS: the blue spot formed is indicative of the presence of retinol. The approximate R_f values of the predominant spots, corresponding to the different forms of retinol, are: (*alcohol* form) 0.1; (*acetate*) 0.45; and (*palmitate*) 0.7.

Absorbance ratio—The ratio of the corrected absorbance [A_{325}] to the observed absorbance A_{325} determined as directed under *Vitamin A Assay*, page 632, is not less than 0.85.

Assay—Using a suitable quantity of Vitamin A, accurately weighed, proceed as directed under *Vitamin A Assay*, page 632.

Vitamin A Capsules

Category: Vitamin A (anti-xerophthalmic).

Usual dose:

Prophylactic—1.5 mg (5000 USP Vitamin A Units) once a day.

Therapeutic—3 to 15 mg (10,000 to 50,000 Units) once a day.

Usual dose range:

Prophylactic—1.5 to 2.4 mg (5000 to 8000 Units) once a day.

Therapeutic—3 to 150 mg (10,000 to 500,000 Units) once a day.

Usual pediatric dose:

Prophylactic—The following amounts once a day:

Infants up to one year of age: 450 µg (1500 Units).

One to three years: 600 µg (2000 Units).

Three to six years: 750 µg (2500 Units).

Six to ten years: 1.05 mg (3500 Units).

Ten to twelve years: 1.35 mg (4500 Units).

Twelve years and over: See *Usual dose*.

Therapeutic—See *Usual dose*.

* Patented. See notice, page iv.

† NOTE—One USP Vitamin A Unit is the specific biologic activity of 0.3 µg of the all-*trans* isomer of retinol.

Capsules available—Capsules usually available contain the following amounts of vitamin A: 1.5, 7.5, and 15 mg (5000, 25,000, and 50,000 Units).

Dispensing information—

Advice: Notify physician if signs of hypervitaminosis A (anorexia, drying or cracking of skin or lips, irritability, headache, loss of hair) occur.

» Vitamin A Capsules contain not less than 95.0 percent and not more than 120.0 percent of the labeled amount of vitamin A.

Packaging and storage—Preserve in tight, light-resistant containers.

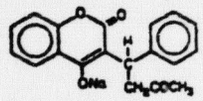
Labeling—Label Capsules to indicate the form in which the vitamin is present, and to indicate the vitamin A activity in terms of the equivalent amount of retinol in mg and in USP Vitamin A Units per Capsule.

Content uniformity, page 648: meet the requirements for *Capsules*.

Other requirements—The contents of Capsules respond to the *Identification tests* and meet the requirements of the test for *Absorbance ratio* under *Vitamin A*, page 537.

Assay—Using not less than 5 Vitamin A Capsules, proceed as directed under *Vitamin A Assay*, page 632. Calculate the content of retinol ($C_{20}H_{30}O$) in mg and in USP Vitamin A Units per Capsule.

Warfarin Sodium



$C_{19}H_{15}NaO_4$ 330.31

2*H*-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-, sodium salt.

3-(α-Acetonylbenzyl)-4-hydroxycoumarin sodium salt [*129-06-6*].

Category: See *Warfarin Sodium for Injection; Warfarin Sodium Tablets*.

Description: White, odorless, amorphous or crystalline powder, having a slightly bitter taste. Is discolored by light.

Solubility: Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether.

» Warfarin Sodium is an amorphous solid or a crystalline clathrate. The clathrate form consists principally of warfarin sodium, isopropyl alcohol, and water, the molecular proportions of which vary between 8:4:0 and 8:2:2. Warfarin Sodium contains not less than 97.0 percent and not more than 102.0 percent of $C_{19}H_{15}NaO_4$, calculated on the anhydrous and isopropyl alcohol-free basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Labeling—Label it to indicate whether it is the amorphous or the crystalline form.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of the residue obtained in *Identification test B* exhibits maxima only at the same wavelengths as that of a similar preparation of USP Warfarin Reference Standard.

B: Dissolve about 100 mg in 25 ml of water, and adjust with hydrochloric acid to a pH of less than 3, using short-range pH indicator paper. Filter the mixture, wash the precipitate with four 5-ml portions of water, and dry at 105° for 1 hour: the warfarin so obtained melts between 157° and 167°, but the range between beginning and end of melting does not exceed 4°.

C: The filtrate obtained in *Identification test B* responds to the tests for *Sodium*, page 617.

pH, page 653: between 7.2 and 8.3, in a solution (1 in 100).

Water, *Method I*, page 668: not more than 4.5%.

Heavy metals, page 619—Dissolve 4 g in 45 ml of water, add 5 ml of glacial acetic acid, stir until the precipitate agglomerates, filter, and use 25 ml of the filtrate, employing glacial acetic acid, if necessary, to make the pH adjustment: the limit is 0.001%.

Absorbance in alkaline solution—Dissolve 1.25 g, accurately weighed, in 10 ml of sodium hydroxide solution (1 in 20), filter through a membrane filter, and within 15 minutes determine the absorbance of the solution in a 1-cm cell at 385 nm, with a suitable spectrophotometer, using sodium hydroxide solution (1 in 20) as the blank: the absorbance does not exceed 0.1.

Isopropyl alcohol (if present)—Dissolve about 800 mg, accurately weighed, in 25.0 ml of water in a conical flask. Add 25.0 ml of dilute sulfuric acid (3 in 200) while swirling, filter, and pipet 10 ml of the clear filtrate into a 250-ml flask containing 40 ml of water. Add a boiling aid such as silicon carbide, then add 30 ml of a 1 in 10 solution of potassium dichromate in dilute sulfuric acid (1 in 5), and connect the flask to a condenser by means of a 75-mm connecting tube. Distil 60 ml, collecting the distillate in 20 ml of sodium hydroxide solution (2 in 25) contained in a 250-ml iodine flask immersed in an ice bath. Add, with swirling, 20.0 ml of 0.1 *N* iodine, insert the stopper in the flask, and allow to stand for 30 minutes. Add 5 ml of hydrochloric acid through the well in the flask, rinse the well and the neck of the flask with water, swirl to mix, remove the stopper, and titrate the excess iodine with 0.1 *N* sodium thiosulfate, adding 3 ml of starch TS as the end-point is approached. Each ml of 0.1 *N* iodine consumed is equivalent to 1.001 mg of isopropyl alcohol. Not less than 4.3% and not more than 8.3% is found.

Assay—Weigh accurately about 110 mg of Warfarin Sodium, transfer to a 100-ml volumetric flask, add sodium hydroxide solution (1 in 2500) to volume, and mix. Pipet 10 ml of this solution into a 1000-ml volumetric flask, add sodium hydroxide solution (1 in 2500) to volume, and mix. Dissolve 25 mg of USP Warfarin Reference Standard, previously dried in vacuum over phosphorus pentoxide for 4 hours and accurately weighed, in 2.5 ml of sodium hydroxide solution (1 in 250), and dilute with water to 25.0 ml. Pipet 10 ml of this solution into a 1000-ml volumetric flask, and add sodium hydroxide solution (1 in 2500) to volume to obtain a Standard solution having a known concentration of about 10 μg per ml. Concomitantly determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 308 nm, with a suitable spectrophotometer, using sodium hydroxide solution (1 in 2500) as the blank. Calculate the quantity, in mg, of $C_{19}H_{15}NaO_4$ in the portion of Warfarin Sodium taken by the formula $10C(1.071A_U/A_S)$, in which C is the concentration, in μg per ml, of USP Warfarin Reference Standard in the Standard solution, 1.071 is the ratio of the molecular weight of warfarin sodium to that of warfarin, and A_U and A_S are the absorbances of the solution of Warfarin Sodium and the Standard solution, respectively.

Warfarin Sodium for Injection

Category: Anticoagulant.

Usual dose:

Initial—Intramuscular or intravenous, 40 to 60 mg.

Maintenance—5 to 10 mg once a day, as indicated by prothrombin-time determinations.

Usual dose range:

Initial—20 to 60 mg.

Maintenance—2 to 10 mg daily.

Sizes available—It is usually available containing the following amounts of warfarin sodium: 50 and 75 mg.

on sterile dry solids or liquid concentrates. However, in the interest of assuring the quality of injection preparations as they are actually administered, the following non-destructive tests are provided for demonstrating the suitability of constituted solutions when they are prepared just prior to use.

Completeness and Clarity of Solution—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form.

A: The solid dissolves completely, leaving no visible residue as undissolved matter.

B: The constituted solution is not significantly less clear than an equal volume of the diluent or of purified water (see page 540) contained in a similar vessel and examined similarly.

Particulate Matter—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form: the solution is essentially free from particles of foreign matter that can be observed on visual inspection.

USP REFERENCE STANDARDS

Reference Standards are specifically required in many Pharmacopeial assays and tests. Originally introduced for the biological assays of USP X, the use of reference standards has been extended to the point where they are now required for numerous other Pharmacopeial assays as well.

USP Reference Standards are substances selected for their high purity, critical characteristics, and suitability for the intended purpose. Heterogeneous substances, of natural origin, also are designated "Reference Standards" where needed. Usually these are the counterparts of international standards. Neither Reference Standards nor Authentic Substances are intended for use as drugs.

USP Reference Standards are established and released under the authority of the USPC Board of Trustees upon recommendation of the USP Reference Standards Committee, which passes on the selection and suitability of each lot. The critical characteristics of each lot of specimen selected for the standard are usually determined independently in three or more laboratories. The Drug Standards Laboratory (see *Preface*) and the Food and Drug Administration laboratories participate in testing almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the nation, both academic and industrial, participate in the testing.

Reference Standards for biologicals are prepared and distributed by the Bureau of Biologics, Food and Drug Administration.

A program to provide international biological standards and chemical reference substances is maintained by the World Health Organization, an agency of the United Nations. The WHO program is concerned with reference materials for antibiotics, biologicals, and chemotherapeutic agents. As a rule, an International Standard for a material of natural origin is discontinued once the substance responsible for its characteristic activity has been isolated, identified, and prepared in such form that it can be completely characterized by chemical and physical means. The USP Reference Standards Committee collaborates closely with the WHO in order to minimize unavoidable differences in the actual units of potency, and in some cases to share in the preparation of a reference standard. Since some USP Reference Standards are standardized in terms of the corresponding International Standards, the relevant USP Units and the International Units of potency are generally identical.

As a service, the USPC tests and distributes specimens of narcotics and other controlled substances. These materials, and some Reference Standards formerly required in the Pharmacopeial assays and tests, are available as Authentic Substances for use as needed in nonofficial assays. The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration of the Department of Justice.

As an additional service, the USPC distributes several noncommercial reagents required in certain USP monographs. These reagents are specially prepared for their intended use and are distributed by USPC only until they become commercially available.

No radioactive USP Reference Standards are provided, because of the special circumstances surrounding the preparation, storage, and distribution of standardized forms of radioactive substances suitable for use in drug analyses. Reliable standards of some radioactive substances, including chromium 51, cobalt 60, gold 198, iodine 131, and phosphorus 32, are available upon order from commercial sources.

Proper Use of USP Reference Standards—In order to serve the intended purpose, it is essential that each USP Reference Standard be properly stored, handled, and used. Generally, Reference Standards should be stored away from heat and protected from light. Where special storage conditions are necessary, directions are given on the label.

Numerous Pharmacopeial tests and assays are based upon comparison of a test specimen with a USP Reference Standard. In such cases, measurements are made on preparations of both the test specimen and the Reference Standard. Where it is directed that a Standard solution or a *Standard preparation* be prepared for a quantitative determination by stepwise dilution or otherwise, it is intended that the Reference Standard substance shall be accurately weighed, with due account being taken of the relatively large errors associated with weighing small masses (see also *Dilution* on page 5 under *General Notices*).

Periodically, the USPC publishes the current list of Reference Standards and Authentic Substances and their corresponding lot designations. It is the responsibility of the analyst to ascertain that his particular supply of USP Reference Standard is current.[1]

[1] The current list is available from: USP Reference Standards, 12601 Twinbrook Parkway, Rockville, Md. 20852.

The following USP Reference Standards are available (the Melting Point Standards are shown in *italics*, where listed individually).

5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid
Acetaminophen
Acetanilid
Acetazolamide
Acetohexamide
α-*d*-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane
Allopurinol
Aminobutanol
3-Amino-4-carboxamidopyrazole Hemisulfate
3-Amino-2,4,6-triiodobenzoic Acid
5-Amino-2,4,6-triiodo-*N*-methylisophthalamic Acid
Amitriptyline Hydrochloride
Amobarbital
Amodiaquine Hydrochloride
Amphotericin B
Ampicillin
9,11-Anhydroprednisolone Tebutate
Anthralin
Ascorbic Acid
Aspirin
Atropine Sulfate
Azathioprine
Bacitracin Zinc
Benzalkonium Chloride
Gamma Benzene Hexachloride
Benzoic Acid
Hydrous Benzoyl Peroxide
Benztropine Mesylate
Bephenium Hydroxynaphthoate
Betazole Hydrochloride
Bisacodyl
4,4'-Bis[4-(*p*-chlorophenyl)-4-hydroxypiperidino]butyrophenone
Butylparaben
Caffeine
Caffeine
Calcium Pantothenate
Capreomycin Sulfate
Carbachol
Carbamazepine
Carbenicillin Monosodium Monohydrate
Cephalexin
Cephalothin Sodium
Ceryl Alcohol
Chlorambucil
Chloramphenicol
Chlordiazepoxide Hydrochloride
Chlorobenzenes
Chloroquine Phosphate

Chlorothiazide
4-Chloro-3-sulfamoylanthranilic Acid
Chlorpheniramine Maleate
Chlorpromazine Hydrochloride
Chlorpropamide
Chlorthalidone
Cholecalciferol
Cholesteryl Caprylate
Cholestyramine Resin
Chymotrypsin
Clindamycin Hydrochloride
Clofibrate
Clomiphene Citrate
Cloxacillin Sodium
Codeine Phosphate
Colchicine
Colistimethate Sodium
Colistin Sulfate
Corticotropin
Cortisone Acetate
Cyanocobalamin
Cyclizine Hydrochloride
Cyclopentolate Hydrochloride
Cyclophosphamide
Cycloserine
Cytarabine
Danthron
Dapsone
Desoxycorticosterone Acetate
Dexamethasone
Dexamethasone Phosphate
Dextroamphetamine Sulfate
Diacetylfluorescein
Diatrizoic Acid
Diazepam
Diazoxide
Dichlorphenamide
Dicloxacillin Sodium
Dicumarol[2]
Dicyclomine Hydrochloride
Diethylcarbamazine Citrate
Diethylstilbestrol
Digitoxin
Digoxin
Dihydrotachysterol
Diiodohydroxyquin
Dimenhydrinate
α-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride
Dioctyl Sodium Sulfosuccinate
Dioxybenzone
Diphenhydramine Hydrochloride
Diphenoxylate Hydrochloride
Doxycycline Hyclate
Edetate Calcium Disodium
Edetate Disodium
Edrophonium Chloride
Emetine Hydrochloride
Ephedrine
Epinephrine Bitartrate
Equilin
Ergocalciferol
Ergonovine Maleate
Ergosterol
Erythromycin
Erythromycin Ethylsuccinate
Erythromycin Gluceptate
Erythromycin Lactobionate
Erythromycin Stearate
Erythrosine Sodium
Estradiol Cypionate
Estradiol Valerate
Estrone
Ethacrynic Acid
Ethambutol Hydrochloride
Ethinyl Estradiol
Ethionamide
Ethopropazine Hydrochloride
Ethosuximide
Ethoxzolamide
Ethylparaben
Ethynodiol Diacetate

[2] Formerly called Bishydroxycoumarin.

Evans Blue
Fentanyl Citrate
Fluoxymesterone
Fludrocortisone Acetate
Fluocinolone Acetonide
Fluorouracil
Fluoxymesterone
Fluphenazine Enanthate
Fluphenazine Dihydrochloride
Fluphenazine Hydrochloride
Flurandrenolide
Folic Acid
Furosemide
Gallamine Triethiodide
Gentamicin Sulfate
Gentian Violet
Globin
Glucagon
Chorionic Gonadotropin
Griseofulvin
Guanethidine Sulfate
Haloperidol
Heparin Sodium
Hexachlorophene
Histamine Dihydrochloride
Homatropine Hydrobromide
Hydralazine Hydrochloride
Hydrochlorothiazide
Hydrocortisone
Hydrocortisone Acetate
Hydrocortisone Hemisuccinate
Hydrocortisone Phosphate
Hydrocortisone Phosphate Triethylamine
Hydrocortisone Tebutate
Hydroquinone
Hydroxychloroquine Sulfate
Hydroxyprogesterone Caproate
Hydroxypropyl Methylcellulose
Hydroxystilbamidine Isethionate
Idoxuridine
Imipramine Hydrochloride
Indigotindisulfonate Sodium
Indocyanine Green
Insulin
Iodipamide
Iothalamic Acid
Ipodate Calcium
Ipodate Sodium
Isoproterenol Hydrochloride
Diluted Isosorbide Dinitrate
Kanamycin Sulfate
Leucovorin Calcium
Levarterenol Bitartrate
Levodopa
Levothyroxine
Lidocaine
Lincomycin Hydrochloride
Liothyronine
Lithium Carbonate
Mafenide Acetate
Magaldrate
Meclizine Hydrochloride
Medroxyprogesterone Acetate
Medrysone
Melting Point Standards
Acetanilid
Caffeine
Phenacetin
Sulfanilamide
Sulfapyridine
Vanillin
Meperidine Hydrochloride
Mepivacaine Hydrochloride
Meprobamate
Mercaptopurine
Mestranol
Metaraminol Bitartrate
Methadone Hydrochloride
Methazolamide
Methicillin Sodium
Methimazole
Methohexital
Methotrexate
Methoxamine Hydrochloride
Methoxsalen

3-Methoxytyrosine
Methylcellulose
Methyldopa
Methyldopate Hydrochloride
Methylene Blue
Methylparaben
Methylphenidate Hydrochloride
Methylphenidate Hydrochloride Erythro Isomer
Methylprednisolone Acetate
Methylprednisolone Hemisuccinate
Methyltestosterone
Methysergide Maleate
Metronidazole
Metyrapone
Minocycline Hydrochloride
Mitotane
Morphine Sulfate
Nafcillin Sodium
Naloxone
Naphazoline Hydrochloride
Neomycin Sulfate
Neostigmine Bromide
Neostigmine Methylsulfate
Niacinamide
Nitrofurantoin
Norethindrone
Norethindrone Acetate
Norgestrel
Noroxymorphone Hydrochloride
Novobiocin
Nystatin
Ouabain
Oxacillin Sodium
Oxybenzone
Oxymetazoline Hydrochloride
Oxytetracycline
Palmitic Acid
Paramethadione
Penicillamine
Penicillin G Benzathine
Penicillin G Sodium
Penicillin V[3]
Pentobarbital
Phenacetin
Phenformin Hydrochloride
Phenobarbital
Phentolamine Mesylate
Phenylbutazone
Phenylephrine Hydrochloride
Phenytoin[4]
Physostigmine Salicylate
Phytonadione
Pilocarpine Nitrate
Negative Control Plastic
Polymyxin B Sulfate
Posterior Pituitary
Pralidoxime Chloride
Prednisolone
Prednisolone Acetate
Prednisolone Succinate
Prednisolone Tebutate
Prednisone
Prednisone Tebutate
Primidone
Probenecid
Procaine Hydrochloride
Procarbazine Hydrochloride
Prochlorperazine Maleate
Progesterone
Promethazine Hydrochloride
Proparacaine Hydrochloride
Propoxyphene Hydrochloride
Propranolol Hydrochloride
Propylparaben
Propylthiouracil
Protamine
Pyrazinamide
Pyridostigmine Bromide

[3] Formerly called Penicillin Phenoxymethyl.

[4] Formerly called Diphenoxtoin.

Pyridoxine Hydrochloride
Pyrimethamine
Pyrvinium Pamoate
Quinacrine Hydrochloride
Quinidine Gluconate
Quinine Sulfate
Reserpine
Resorcinol
Riboflavin
Rifampin
Salicylic Acid
Scopolamine Hydrobromide
Secobarbital
Sodium Fluoride
Spectinomycin Hydrochloride
Spironolactone
Stearic Acid
Stearyl Alcohol
Streptomycin Sulfate
Sulfacetamide Sodium
Sulfadiazine
Sulfamerazine
Sulfamethazine
Sulfanilamide
Sulfanilamide
Sulfapyridine
Sulfapyridine
Sulfinpyrazone
Sulfisoxazole
Sulfisoxazole Acetyl
Sulfobromophthalein Sodium
Testosterone Cypionate
Testosterone Enanthate
Testosterone Propionate
Tetracaine Hydrochloride
Tetracycline Hydrochloride
Tetrahydrozoline Hydrochloride
Theophylline
Thiabendazole
Thiamine Hydrochloride
Thioguanine
Thiopental
Thioridazine Hydrochloride
Tolazamide
Tolbutamide
Tolnaftate
o-Toluenesulfonamide } Supplied
p-Toluenesulfonamide } in a set.
Tretinoin
Triamcinolone Acetonide
Triamcinolone Hexacetonide
Triamterene
Trihexyphenidyl Hydrochloride
3,4,6-Trihydroxyphenylalanine
Trimeprazine Tartrate
Trimethadione
Trimethaphan Camsylate
Trioxsalen
Tripelennamine Citrate
Tripelennamine Hydrochloride
Tropicamide
Trypsin Crystallized
Tubocurarine Chloride
Vancomycin Hydrochloride
Vanillin
Vanillin
Vinblastine Sulfate
Vincristine Sulfate
Viomycin Sulfate
Vitamin A
Warfarin

Apparatus for Tests and Assays

THERMOMETERS

Thermometers suitable for Pharmacopeial tests conform to specifications of the American Society for Testing and Materials, ASTM Standards E 1, and are standardized in accordance with ASTM Method E 77.

The thermometers are of the mercury-in-glass type, and the column above the liquid is filled with nitrogen. Thermometers may be standardized for total immersion or for partial immersion. Insofar as practicable, each thermometer should be employed according to the condition of immersion under which it was standardized.

Standardization for total immersion involves immersion of the thermometer to the top of the mercury column, with the remainder of the stem and the upper expansion chamber exposed to ambient temperature. Standardization for partial immersion involves immersion of the thermometer to the indicated immersion line etched on the front of the thermometer, with the remainder of the stem exposed to ambient temperature. For use under other conditions of immersion, an emergent stem correction is necessary to obtain correct temperature readings.

In the selection of a thermometer, careful consideration of the conditions under which it is to be used is essential. The accompanying table lists specifications for a number of thermometers suitable for use in Pharmacopeial tests. The lower and upper limits of temperature range specified in the table are to be regarded as inclusive.

Thermometer Specifications

ASTM No. E 1	Temperature Range (°C)	Graduations (°C)	Immersion (mm)
Thermometers for General Use, Including Melting Range Determinations			
1C	−20 to 150	1	76
2C	−5 to 300	1	76
3C	−5 to 400	1	76

Thermometer Specifications—Continued

ASTM No. E 1	Temperature Range (°C)	Graduations (°C)	Immersion (mm)
Thermometers for Boiling or Distilling Range or Temperature Determinations			
37C	−2 to 52	0.2	100
38C	24 to 78	0.2	100
39C	48 to 102	0.2	100
40C	72 to 126	0.2	100
41C	98 to 152	0.2	100
102C	123 to 177	0.2	100
103C	148 to 202	0.2	100
104C	173 to 227	0.2	100
105C	198 to 252	0.2	100
106C	223 to 277	0.2	100
107C	248 to 302	0.2	100
Thermometers for Congealing Range or Temperature Determinations			
89C	−20 to 10	0.1	76
90C	0 to 30	0.1	76
91C	30 to 50	0.1	76
92C	40 to 70	0.1	76
93C	60 to 90	0.1	76
94C	80 to 110	0.1	76
95C	100 to 130	0.1	76
96C	120 to 150	0.1	76

NOTE—The revised centigrade scale attributed to Celsius differs slightly from the so-called centigrade scale heretofore accepted. However, the magnitude of the difference is negligible, and the two scales are considered equally suitable for Pharmacopeial purposes.

436a

NATIONAL FORMULARY XIV

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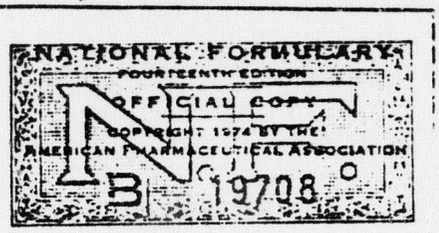

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Cod Liver Oil

CATEGORY—Source of vitamins A and D.

USUAL DOSE—5 ml containing 1170 μg (3900 USP Units) of vitamin A and 9.7 μg (386 USP Units) of vitamin D.

NOTE: Cod Liver Oil containing more than the minimum NF requirements for both vitamin A and vitamin D may be administered in proportionally smaller doses.

DESCRIPTION—Cod Liver Oil is a thin, oily liquid, having a characteristic, slightly fishy but not a rancid odor, and a fishy taste.

SOLUBILITY—Cod Liver Oil is slightly soluble in alcohol. It is freely soluble in ether, in chloroform, in carbon disulfide, and in ethyl acetate.

Cod Liver Oil is the partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of the Family Gadidae. Cod Liver Oil contains, in each g, not less than 255 μg (850 USP Units) of vitamin A and not less than 2.125 μg (85 USP Units) of vitamin D.

Cod Liver Oil may be flavored by the addition of not more than 1 percent of a suitable flavoring substance or a mixture of such substances.

Packaging and storage—Preserve Cod Liver Oil in tight containers. It may be bottled or packaged in containers from which air has been expelled by the production of a vacuum or by an inert gas.

Labeling—The vitamin A potency and vitamin D potency of Cod Liver Oil, when designated on the label, are expressed in United States Pharmacopeia Units per g of oil. These units may be referred to as USP Units.

Reference standards—

USP Vitamin D Capsules Reference Standard—Keep container tightly closed and protected from light, and store in a refrigerator.

Identification for vitamin A—To 1 ml of a chloroform solution of Cod Liver Oil (1 in 40) add 10 ml of antimony trichloride TS: a blue color results immediately.

Specific gravity, page 963—The specific gravity of Cod Liver Oil is between 0.918 and 0.927.

Color—When viewed transversely in a tall, cylindrical, standard oil-sample bottle of colorless glass of about 120-ml capacity, the color of Cod Liver Oil is not more intense than that of a mixture of 11 ml of cobaltous chloride CS, 76 ml of ferric chloride CS, and 33 ml of water, in a similar bottle of the same internal diameter.

Nondestearinated cod liver oil—Fill a tall, cylindrical, standard oil-sample bottle of about 120-ml capacity with Cod Liver Oil at a temperature between 23 and 28°, stopper, and immerse the bottle in a mixture of ice and water for 3 hours: the oil remains clear and does not deposit stearin.

Unsaponifiable matter, page 896—Cod Liver Oil contains not more than 1.30% of unsaponifiable matter.

Acid value—Mix 15 ml of alcohol with 15 ml of ether, add 5 drops of phenolphthalein TS, and neutralize with 0.1 *N* sodium hydroxide. Dissolve 2 g of Cod Liver Oil, accurately weighed, in the mixture, and boil the oil solution gently under a reflux condenser for 10 minutes. Cool, and titrate the mixture with 0.1 *N* sodium hydroxide to the production of a pink color which persists after shaking for 30 seconds: not more than 1 ml of 0.1 *N* sodium hydroxide is required.

Iodine value, page 896—The iodine value of Cod Liver Oil is between 145 and 180.

Saponification value, page 896—The saponification value of Cod Liver Oil is between 180 and 192. If carbon dioxide has been used as a preservative, expose the Oil in a shallow dish in a vacuum desiccator for 24 hours before weighing the sample for determination of the saponification value.

Assay for vitamin A—Using an accurately weighed sample of 500 mg to 1 g of Cod Liver Oil, proceed as directed under *Vitamin A Assay*, page 994.

Assay for vitamin D—Proceed as directed under *Vitamin D Assay, Biological Method*, page 998.

Compound Iodochlorhydroxyquin Powder, page 359
Compound Resorcinol Ointment, page 637

rly measured, and the respec-
ivities, calculated on the dried
point of maximum absorbance
t about 277 nm, do not differ
n 3.0%.
925—The pH of a solution of
drochloride (1 in 100) is be-
nd 6.5.
rying, page 906—Dry Nylidrin
ide in vacuum at 60° for 3
oes not more than 0.5% of its
on Ignition, page 955—The
c.
ransfer about 700 mg of
Hydrochloride, accurately
a 150-ml tall-form beaker.
of glacial acetic acid, and heat
bath until solution is complete.
of mercuric acetate TS, cool,
s of crystal violet TS, and
0.1 *N* perchloric acid to a
point. Perform a blank de-
, and make any necessary
Each ml of 0.1 *N* perchloric
valent to 33.59 mg of $C_{18}H_{23}$-

njection

ion usually available contains
in 1 ml and 50 mg in 10 ml.

solution of nylidrin
ntains not less than
cent of the labeled

ne of Nylidrin Hydrochloride
quivalent to about 40 mg of
drochloride, to a 125-ml sepa-
dilute to 35 ml with water.
sodium carbonate TS, and ex-
lution with four 10-ml portions
orm. Wash the combined
extracts with 10 ml of water,
xtract the wash solution with
oroform. Filter the combined
extracts through a tightly
loroform-washed pledget of
. wash the cotton with 5 ml of
Add methanolic methyl red
hloroform solution, and titrate
N perchloric acid in dioxane.
lank determination, and make
ary correction. Each ml of
chloric acid is equivalent to
$C_{18}H_{23}NO_2 \cdot HCl$.

Tablets

usually available contain the
mg.

Nylidrin Hydrochloride Tablets contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of $C_{18}H_{23}NO_2 \cdot HCl$.

Packaging and storage—Preserve Nylidrin Hydrochloride Tablets in tight containers.

Reference standards—

NF Nylidrin Hydrochloride Reference Standard—Dry in vacuum at 60° for 3 hours before using.

Identification—Transfer an amount of powdered Nylidrin Hydrochloride Tablets, equivalent to about 100 mg of nylidrin hydrochloride, to a 60-ml separator, add 20 ml of water, and proceed as directed in *Identification test C* under *Nylidrin Hydrochloride*, page 497, beginning with "... add 5 ml of sodium carbonate TS."

Disintegration, page 978—The disintegration time limit for Nylidrin Hydrochloride Tablets is 30 minutes.

Content uniformity, page 889—Nylidrin Hydrochloride Tablets meet the requirements of the content uniformity test for tablets, using the following special procedure: Quantitatively transfer a finely powdered tablet to a 100-ml volumetric flask, add tribasic sodium phosphate solution (1 in 50) to volume, mix, and centrifuge a portion of the mixture at high speed. Dilute an accurately measured volume of the supernatant liquid quantitatively and stepwise, if necessary, with the phosphate solution to provide a solution containing approximately 10 µg of nylidrin hydrochloride per ml. Concomitantly determine the absorbance of this solution and of a solution of NF Nylidrin Hydrochloride Reference Standard, in the same medium at a concentration of about 10 µg per ml, in 1-cm cells, at the maximum at about 242 nm, with a suitable spectrophotometer, using the phosphate solution as the blank. Calculate the quantity, in mg, of $C_{18}H_{23}NO_2 \cdot HCl$ in the tablet by the formula:

$$(TC/D)(A_U/A_S)$$

in which T is the labeled quantity, in mg, of nylidrin hydrochloride in the tablet; C is the exact concentration, in µg per ml, of the Reference Standard solution; D is the exact concentration, in µg per ml, of nylidrin hydrochloride in the sample solution, based upon the labeled quantity per tablet and the extent of dilution; A_U is the absorbance of the sample solution; and A_S is the absorbance of the Reference Standard solution.

Assay—Weigh and finely powder not less than 20 Nylidrin Hydrochloride Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of nylidrin hydrochloride, to a 125-ml separator. Add 35 ml of water and 5 ml of sodium carbonate TS, and proceed as directed in the *Assay* under *Nylidrin Hydrochloride Injection*, page 498, beginning with "... extract the solution with four 10-ml portions of chloroform."

Oleovitamin A and D

CATEGORY—Source of vitamins A and D.

USUAL DOSE—To be determined by the practitioner, according to the needs of the patient.

DESCRIPTION—Oleovitamin A and D occurs as a yellow to red, oily liquid. It is a clear liquid at temperatures above 65°, and it may crystallize on cooling. Oleovitamin A and D may be nearly odorless or may have a fish-like odor. It does not have a rancid odor or taste. It is unstable in air and in light.

SOLUBILITY—Oleovitamin A and D is insoluble in water and in glycerin. It is soluble in dehydrated alcohol and in vegetable oils, and is very soluble in ether and in chloroform.

Oleovitamin A and D is a solution of vitamin A and vitamin D in fish liver oil or in an edible vegetable oil. The vitamin D is present as ergocalciferol or cholecalciferol obtained by the activation of ergosterol or 7-dehydrocholesterol or from natural sources. Oleovitamin A and D contains not less than 90.0 percent of the labeled amounts of vitamins A and D.

Packaging and storage—Preserve Oleovitamin A and D in tight containers, protected from light and air, preferably under an atmosphere of an inert gas. Store in a dry place.

Labeling—Label Oleovitamin A and D to indicate the content of vitamin A in mg per g. The vitamin A content may also be expressed in USP Units of vitamin A per g. Label Oleovitamin A and D to

show whether it contains ergocalciferol, cholecalciferol, or vitamin D from a natural source. State the vitamin D content in µg per g. Its vitamin D content may also be expressed in USP Units of vitamin D per g.

Reference standards—

USP Vitamin D Capsules Reference Standard—Keep container tightly closed and protected from light, and store in a refrigerator.

Identification for vitamin A—Dilute sufficient Oleovitamin A and D with chloroform so that approximately 6 µg of vitamin A is contained in each ml of the solution. To 1 ml of this solution add 10 ml of antimony trichloride TS: a blue color appears at once.

Assay for vitamin A—Proceed as directed under *Vitamin A Assay*, page 994.

Assay for vitamin D—Accurately measure a portion of Oleovitamin A and D expected to contain about the equivalent of 125 to 250 µg of vitamin D, but not more than 7.5 mg of vitamin A, and proceed as directed under *Vitamin D Assay, Chemical Method*, page 1000. If the sample contains less than the equivalent of 2.5 µg of vitamin D per g, or if the ratio of vitamin A to vitamin D exceeds 300 to 1, proceed as directed under *Vitamin D Assay, Biological Method*, page 998.

Oleovitamin A and D Capsules

CATEGORY and DOSE—See Oleovitamin A and D.

DESCRIPTION—The oil contained in Oleovitamin A and D Capsules conforms to the *Description* under *Oleovitamin A and D*, page 499.

Oleovitamin A and D Capsules contain not less than 90.0 percent of the labeled amounts of vitamins A and D. The oil in Oleovitamin A and D Capsules conforms to the definition for *Oleovitamin A and D*, page 499.

Packaging and storage—Preserve Oleovitamin A and D Capsules in tight, light-resistant containers. Store in a dry place.

Labeling—Label Oleovitamin A and D Capsules to indicate the content, in mg, of vitamin A in each capsule. The vitamin A content in each capsule may also be expressed in USP Units of vitamin A. Label Oleovitamin A and D Capsules to show whether they contain ergocalciferol, cholecalciferol, or vitamin D from a natural source. State the vitamin D content, in µg, in each capsule. The vitamin D content may also be expressed in USP Units of vitamin D in each capsule.

Reference standards—

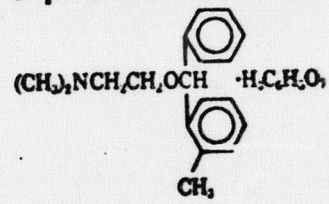
USP Vitamin D Capsules Reference Standard—Keep container tightly closed and protected from light, and store in a refrigerator.

Assay for vitamin A—Transfer to a saponification flask not less than five Oleovitamin A and D Capsules, add 10 to 20 ml of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod, and proceed as directed in the paragraph titled *Saponification* under *Vitamin A Assay*, page 994, beginning with "Reflux in an *all-glass* apparatus...."

Assay for vitamin D—Transfer to a saponification flask not less than five Oleovitamin A and D Capsules, add 10 to 20 ml of water, and heat for about 10 minutes. Crush any remaining solids with the blunt end of a glass rod, and proceed as directed under *Vitamin D Assay, Chemical Method*, page 1000.

The *Sample Preparation* used in the chromatographic procedures must contain not more than the equivalent of 7.5 mg of vitamin A or less than 125 µg of vitamin D. If the ratio of vitamin A to vitamin D in the sample exceeds 300 to 1, proceed as directed under *Vitamin D Assay, Biological Method*, page 998.

Orphenadrine Citrate*

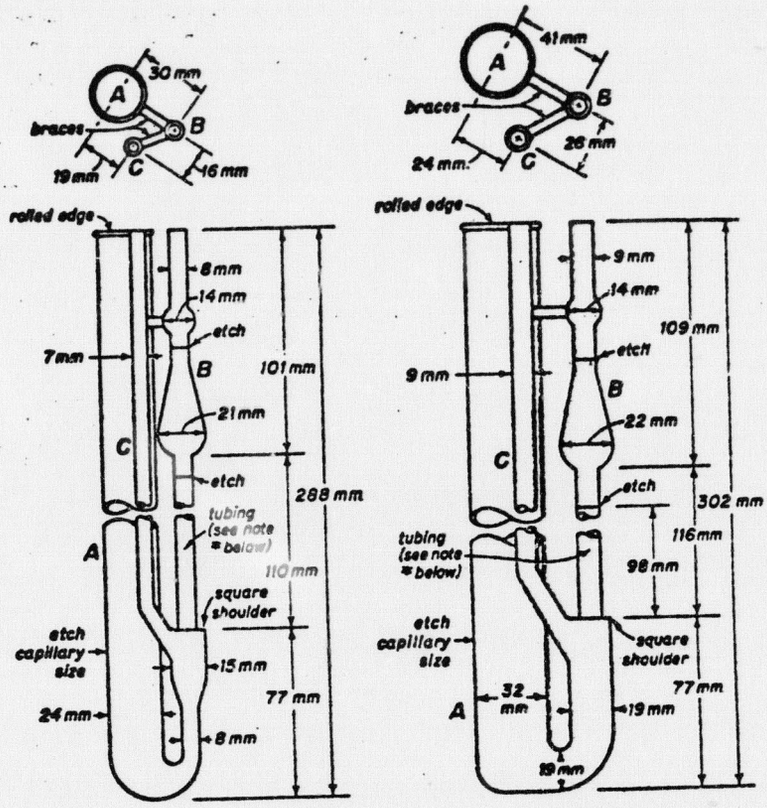


$C_{18}H_{23}NO \cdot C_6H_8O_7$ 461.51

Ethanamine, *N,N*-dimethyl-2-[(2-methylphenyl)phenylmethoxy]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

N,N-Dimethyl-2-[(*o*-methyl-α-phenylbenzyl)oxy]ethylamine citrate (1:1) [4682-36-4]

* Patented. See notice, page ii.



Viscosimeter for Low Viscosity
* Precision bore capillary tubing 1.5 mm I.D. for 15-cps, 1.8 mm I.D. for 25-cps, 2.4 mm I.D. for 100-cps, and 3.2 mm I.D. for 400-cps viscosities.

Viscosimeter for High Viscosity
* Precision bore capillary tubing 5.0 mm I.D. for 1500-cps and 6.0 mm I.D. for 4000-cps viscosities.

Viscosimeters Used in Determination of Viscosity of Cellulose Derivatives

for the liquid to flow from the upper mark to the lower mark in the orifice tube.

Calculate the viscosimeter constant, k, from the equation:

$$k = v/dt$$

in which v is the known viscosity, in centipoises, of the liquid, d is the specific gravity of the liquid tested at 20°/20°, and t is the time, in seconds, for the liquid to pass from the upper mark to the lower mark.

If a viscosimeter is repaired, it must be recalibrated, since even minor repairs frequently cause significant changes in the value of its constant, k.

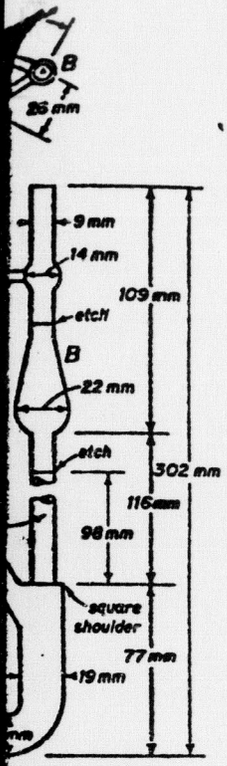
VITAMIN A ASSAY

Complete the assay promptly, and exercise care throughout the procedure to avoid undue exposure to oxidizing agents, to actinic light, and to other conditions that destroy vitamin A. The use of low-actinic glassware is advantageous in avoiding destruction by light.

Isopropyl Alcohol—Use isopropyl alcohol, spectrophotometric grade.

Ether—Use *Ether*, freshly distilled, discarding the first and last 10 percent portions, or *Ether*, anesthetic grade, from a freshly opened container.

Saponification—Transfer to a saponification flask an amount of the sample, accurately measured and expected to contain not less than the equivalent of 150 µg of vitamin A, but not more than 1 g of fat. Reflux in an *all-glass* apparatus with 30 ml of alcohol and 3 ml of potassium hydroxide solution (1 in 2) for 30 minutes. Cool the solution, add 30 ml of



for High Viscosity
capillary tubing 5.0 mm
and 6.0 mm I.D. for
pe viscosities.

ulose Derivatives

quid, *d* is the specific grav-
d tested at 20°/20°, and *t* is
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in an *all-glass* apparatus
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l the solution, add 30 ml of

water, and transfer the resulting solution to a conical separator. Add 2 g of finely powdered sodium sulfate. Extract, by shaking for 2 minutes, with one 150-ml portion of ether, or, if an emulsion occurs, with three additional 25-ml portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 ml of water. Repeat the washing more vigorously until the last washing gives no color with phenolphthalein TS. Transfer the washed ether extract to a 250-ml volumetric flask, and dilute to volume with ether.

Procedure—Evaporate a 25.0-ml aliquot of the ether solution of the unsaponifiable extract to about 5 ml. Without the application of heat, reduce the volume to about 3 ml in a stream of inert gas or under reduced pressure. Dissolve the residue in sufficient *Isopropyl Alcohol* to give an expected concentration of the equivalent of 3 to 5 µg of vitamin A per ml or such that it will give an absorbance in the range 0.4 to 0.8 at 325 nm. Determine the absorbances of the resulting solution, in 1-cm cells, at 310, 325, and 334 nm with a suitable spectrophotometer, using *Isopropyl Alcohol* as the blank.

Calculation—Calculate the vitamin A content, in mg, by the formula:

$$0.549(A_{325}/bC)$$

in which A_{325} is the observed absorbance at 325 nm, b is the length, in cm, of the absorption cell, and C is the amount of sample expressed as g, capsule or tablet, in each 100 ml of the final *Isopropyl Alcohol* solution, provided that A_{325} has a value not less than A_{325}(cor.)/1.030 and not more than A_{325} (cor.)/0.970, where $A_{325}(\text{cor.}) = (6.815A_{325} - 2.555A_{310} - 4.260A_{334})$, in which A designates the absorbance at the wavelengths indicated by the subscripts. Where A_{325}(cor.) has a value less than $A_{325}/1.030$, calculate the vitamin A content, in mg, by the formula:

$$0.549[A_{325(\text{cor.})}/bC]$$

Each mg of vitamin A (alcohol) represents 3333 USP Units of vitamin A.

Confidence Interval—The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P = 0.05$, is approximately ±8 percent.

VITAMIN B_{12} ACTIVITY ASSAY

Reference Standards—

USP Cyanocobalamin Reference Standard—Keep container tightly closed and protected from light. Dry over silica gel for 4 hours before using.

Assay Preparation—Place a suitable quantity of the material to be assayed, accurately measured or weighed, in an appropriate vessel containing, for each g or ml of sample taken, 25 ml of an aqueous extracting solution prepared just prior to use to contain, in each 100 ml, 1.29 g of disodium phosphate, 1.1 g of anhydrous citric acid, and 1.0 g of sodium metabisulfite. Autoclave the mixture at 121° for 10 minutes. Allow any undissolved particles of the sample extract to settle, and filter or centrifuge, if necessary. Dilute an aliquot of the clear solution with water so that the final test solution contains vitamin B_{12} activity approximately equivalent to that of the *Standard Cyanocobalamin Solution* which is added to the assay tubes.

Standard Cyanocobalamin Stock Solution—To a suitable quantity of USP Cyanocobalamin Reference Standard, accurately weighed, add sufficient 25 percent alcohol to make a solution containing, in each ml, 1.0 µg of cyanocobalamin. Store in a refrigerator.

Standard Cyanocobalamin Solution—Dilute a suitable volume of *Standard Cyanocobalamin Stock Solution* with water to a measured volume such that after the incubation period as described under *Procedure*, the difference in transmittance between the inoculated blank and the 5.0-ml level of the *Standard Cyanocobalamin Solution* is not less than that which corresponds to a difference of 1.23 mg in dried cell weight. This concentration usually falls between 0.01 and 0.04 ng per ml of *Standard Cyanocobalamin Solution*. Prepare a fresh standard solution for each assay.

Basal Medium Stock Solution—Prepare the medium according to the following formula and directions. Dehydrated mixtures may be used provided that, when reconstituted as directed in the labeling, they have the same ingredients as, and yield media comparable to, that obtained from the formula given herein.

Add the ingredients in the order listed, carefully dissolving the cystine and tryptophan in the hydrochloric acid before adding the next eight solutions in the resulting solution. Add 100 ml of water, mix, and dissolve the dextrose, sodium acetate, and ascorbic acid. Filter, if necessary, add the polysorbate 80 solution, adjust the reaction to a pH between 5.5 and 6.0 with sodium hydroxide solution (1 in 25), and add purified water to make 250 ml.

L-Cystine	100 mg
L-Tryptophan	50 mg
1 *N* Hydrochloric Acid	10 ml
Adenine–Guanine–Uracil Solution	5 ml
Xanthine Solution	5 ml
Vitamin Solution I	10 ml
Vitamin Solution II	10 ml

mittance for each of the remaining tubes. Disregard the results of the assay if the difference between the transmittance observed at the highest level of the standard and that of the inoculated blank is less than the difference corresponding to a dried cell weight of 1.25 mg per tube.

Calculation—Prepare a standard concentration–response curve by the following procedure. Test for and replace any aberrant individual transmittances. For each level of the standard, calculate the response from the sum of the duplicate values of the transmittance as the difference, $y = 2.00 - \Sigma$ (of transmittance). Plot this response on the ordinate of cross-section paper against the logarithm of the ml of *Standard Cyanocobalamin Solution* per tube on the abscissa, using for the ordinate either an arithmetic or a logarithmic scale, whichever gives the better approximation to a straight line. Draw the straight line or smooth curve which best fits the plotted points.

Calculate the response, y, adding together the two transmittances for each level of the *Assay Preparation*. Read from the standard curve the logarithm of the volume of the *Standard Preparation* corresponding to each of those values of y that falls within the range of the lowest and highest points plotted for the standard. Subtract from each logarithm so obtained the logarithm of the volume, in ml, of the *Assay Preparation* to obtain the difference, x, for each dosage level. Average the values of x for each of three or more dosage levels to obtain $\bar{x} = M'$, the log-relative potency of the *Assay Preparation*. Determine the quantity, in µg, of USP Cyanocobalamin Reference Standard corresponding to the cyanocobalamin in the portion of material taken for assay by the equation:

$$\text{antilog } M = \text{antilog } (M' + \log R)$$

in which R is the number of µg of cyanocobalamin that was assumed to be present in each mg (or capsule or tablet) of the material taken for assay.

Replication—Repeat the entire determination at least once, using separately prepared *Assay Preparations*. If the difference between the two log potencies M is not greater than 0.08, their mean, $\bar{M}$, is the assayed log-potency of the test material (see *Design and Analysis of Biological Assays*, USP XIX). If the two determinations differ by more than 0.08, conduct one or more additional determinations. From the mean of two or more values of M that do not differ by more than 0.15, compute the mean potency of the preparation under assay.

VITAMIN D ASSAY

Biological Method

The biological assay of vitamin D comprises the recording and interpretation of observations on groups of rats maintained on specified dietary regimens throughout specified periods of their lives whereby the biological response to the preparation under assay is compared with the response to NF Vitamin D Capsules Reference Standard.

Reference Standards—

USP Vitamin D Capsules Reference Standard—Keep container tightly closed and protected from light, and store in a refrigerator.

Preliminary Period—Throughout the preliminary period in the life of a rat, which is not longer than 30 days and extends from birth to the first day of the depletion period, maintain litters of rats under the immediate supervision of, or according to the directions of, the individual responsible for the assay. During the preliminary period, use a dietary regimen which provides for normal development but is limited in its content of vitamin D, so that when placed upon the *Rachitogenic Diet* in the depletion period the rats develop rickets. At the end of the preliminary period, reject any rat which weighs less than 44 g or more than 60 g, or which shows evidence of injury, disease, or anatomical abnormality.

Depletion Period—Through the depletion period, which extends from the end of the preliminary period to the first day of the assay period, provide each rat *ad libitum* with the *Rachitogenic Diet* and water, and allow access to no other food or dietary supplement.

Rachitogenic Diet—The *Rachitogenic Diet* consists of a uniform mixture of the following ingredients in the proportions shown in the accompanying table.

Rachitogenic Diet

Ingredient	Parts by weight
Whole yellow corn, ground	76
Wheat gluten, ground	20
Calcium carbonate	3
Sodium chloride	1

When a chemical analysis of the entire ration shows a Ca:P ratio of less than 4:1 or more than 5:1, the proportion of calcium carbonate may be varied to bring the adjusted ratio to a uniform level within this range.

Assigning Rats to Groups for Assay

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$$R = \text{antilog } (M' + \log R)$$

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Rachitogenic Diet

Ingredient	Parts by weight
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...luten, ground	20
...carbonate	3
...hloride	1

...chemical analysis of the entire
...ws a Ca:P ratio of less than 4:1
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Period—Consider a litter suitable for the assay period when individual rats in the litter show evidence of rickets such as enlarged joints and a distinctive wobbly, rachitic gait, provided that the depletion period is not less than 19 or more than 25 days. The presence of rickets may be established also from the width of the rachitic metaphysis upon *X*-ray examination or by applying the line test (described below) to a leg bone of one member of each litter.

Record the weight of each rat, and assign it to a group, in which each rat will be fed a specified dose of the Reference Standard or of an assay sample that is under examination for its vitamin D potency. For each assay sample provide one or more assay groups and at least two standard groups. The two standard groups may be used for the concurrent assay of more than one assay sample. Within an interval not exceeding 30 days, complete the assignment of rats to groups according to a design which divides litters among the groups, to achieve a complete balance.

For complete balance, whereby each litter is represented equally in every group, use seven or more litters containing at least as many depleted rats as there are groups. From a given litter, assign one rat, selected at random, to each group on the same day. If a litter contains twice as many rats as there are groups, assign a second series of rats similarly. The last one or two litters to be assigned may be allotted to groups so that at the start of the assay period the average body weight of any completed groups will not differ by more than 8 g from that of any other group.

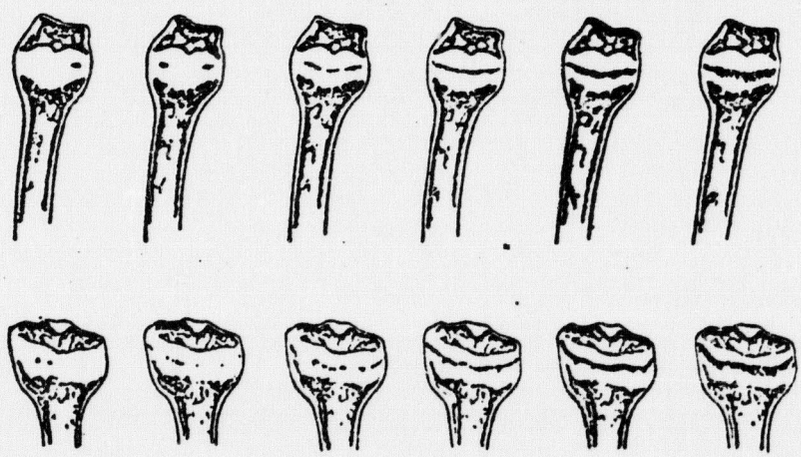
Assay Doses—Select two dosage levels of the USP Vitamin D Capsules Reference Standard, spaced so that the ratio of the larger to the smaller dose is not less than 1.5 or more than 2.5. Select one or two dosage levels based upon a single assumed potency for each sample. The dosage levels of the sample are equivalent to those of the standard or to a mid-level equal to the square root of the product of the two dosage levels of the standard.

Select dosage levels such that, when fed to rachitic rats, they are expected to produce degrees of calcification within the range specified under the test of data acceptability. Before feeding, the Reference Standard and/or sample may be diluted with cottonseed oil, provided that not more than 200 µl is fed on any one day. Store the oil solutions in well-closed bottles, protected from light, at a temperature not exceeding 10°, and use within 5 weeks.

Assign one group of rats to each dosage level of the standard and of the one or more samples.

Assay Period—During the assay period, which extends from the end of the depletion period for a fixed interval of 7 to 10 days, cage each rat individually and provide it *ad libitum* with the *Rachitogenic Diet* and water. Supply a *Rachitogenic Diet* prepared from the same lots of ingredients to all rats. On the first and on the third (or fourth) day of the assay period, feed each rat one-half of its total assigned dose.

Throughout the assay period, maintain as uniform environmental conditions as possible for all rats, and exclude exposure to antirachitic radiations. At the end of a fixed period of 7 to 10 days, weigh and kill each rat. From those rats which do not weigh less at the end than at the start of the assay period and which have consumed each assigned dose within 24 hours of the time it was fed, dissect out



Representative Sections Showing the Radius (upper row) and the Tibia (lower row) in Graded Degrees of Healing in Rachitic Rats within the Useful Range of the Dosage–Response Relationship of the Vitamin D Assay

one or more leg bones for examination by the *Line Test*.

Line Test—Remove the proximal end of a tibia or the distal end of a radius, and clean it of adhering tissue, in any one assay using the same bone from all animals. With a clean, sharp blade cut a median, longitudinal section through the juncture of the epiphysis and diaphysis at the same place on each bone. Rinse both sections in purified water, immerse immediately in silver nitrate solution (1 in 50) for 1 minute, and rinse again in purified water. Expose the cut surface of bone, in water, to daylight or another source of actinic light until the calcified areas develop a clearly defined stain without marked discoloration of the uncalcified areas. The staining procedure may be modified to differentiate more clearly between calcified and uncalcified areas.

Score the degree of calcification of the rachitic metaphysis in each rat, according to a scale which allows the average response to be plotted as a straight line against the logarithm of the dose. The figure presented illustrates the range of the degree of calcification best suited for assay purposes.

Acceptability—Observations are acceptable for use in calculation of the potency only from those groups in which two-thirds or more but not less than seven rats show calcification at least as great as the lowest level and not greater than the highest level illustrated in the figure. If the average score of the standard group on the high dosage level is not greater than the average score of the standard group on the low dosage level, discard the results and repeat the assay. If an assay sample is represented solely by assay groups which are not acceptable for measuring vitamin D potency and in each of which the average score is less than the average score of the standard group on the low dosage level or more than the average score of the standard group on the high dosage level, its assayed content of vitamin D is respectively less than that represented by the low dose or more than that represented by the high dose of the Reference Standard.

Calculation—Tabulate the scores (y), listing each litter in a separate row with treatment groups in columns. Omit any groups which do not meet the test for *Acceptability*. Equalize the number of observations in the acceptable groups by disregarding the results on all litters not equally represented in the groups or by other suitable means (see *Design and Analysis of Biological Assays*, USP XIX). Total the f scores for each of the treatment groups, where f is the number of litters, and designate each total as T with subscripts 1 and 2 for the low and high dosage levels, respectively. Compute the slope b from the sums of T_1, *i.e.*, ΣT_1, and of T_2, *i.e.*, ΣT_2, for the standard and sample, provided the latter is represented at both dosage levels, from the equation:

$$b = (\Sigma T_2 - \Sigma T_1)/ifh'$$

in which i is the logarithm of the ratio of the high dose to the low dose and is the same for each preparation, and h' is the number of preparations represented by two dosage levels and included in the calculation of the value of b.

Compute the logarithm of the relative potency of each sample under assay from the equation:

$$\log (\text{relative potency}) = M' = (\bar{y}_U - \bar{y}_S)/b = ih'T_e/2\Sigma T_t$$

in which each mean score, $\bar{y}_U$ for the assay sample and $\bar{y}_S$ for the Reference Standard, is the average of the individual scores for an intermediate dosage level or of the two means for the high and the low dosage levels and where $T_t = \Sigma T_2 - \Sigma T_1$ and T_e is defined in USP XIX. Convert each observed M' to its antilogarithm to obtain the relative potency of the sample. Multiply the relative potency by the assumed potency of the assay oil in Units per g, adopted at the start of the assay, to obtain its assayed content of vitamin D in USP Units per g.

Chemical Method

The following procedure is provided for the determination of vitamin D as an ingredient of official preparations containing other active constituents.

Reference Standards—

USP Ergocalciferol Reference Standard—Store protected from light in a cold place.

Special Reagents and Solutions—

Chromatographic Fuller's Earth—Use chromatographic fuller's earth having a water content corresponding to not less than 8.5 percent and not more than 9.0 percent of loss on drying.

Solvent Hexane—Use solvent hexane, distilling, if necessary, so that it meets the following additional specification:

Spectral purity—Measure in a 1-cm cell, at 300 nm, with a suitable spectrophotometer, using air as the blank: the absorbance is not more than 0.070.

Ethylene Dichloride—Purify by passage through a column of granular (20 to 200-mesh) silica gel.

Potassium Hydroxide Solution—Dissolve 780 g of potassium hydroxide in water to make 1000 ml.

Cottonseed Oil—Use cottonseed oil USP that meets the following additional requirement: saponify 10 g of the oil as directed in this chapter under *Sample Preparation*, beginning with "...then add a volume of *Potassium Hydroxide Solution*...," and dissolve the unsaponifiable residue in 10 ml of *Solvent Hexane*.

In a separate container place 400 µl of

standard and sample,
is represented at both
om the equation:

$(\Sigma T_2 - \Sigma T_1)/ifh'$

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$= ih'T_s/2\Sigma T_s$

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ical Method

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," and dissolve the unsaponifiable
in 10 ml of *Solvent Hexane*.

separate container place 400 µl of

ferric chloride solution (1 in 1000) and 12 ml of a 1 in 6000 solution of 2,2'-bipyridine in dehydrated alcohol, mix, and 5 minutes later determine the absorbance, in a 1-cm cell, at 520 nm, with a suitable spectrophotometer, using dehydrated alcohol as the blank. Then add 200 µl of the solvent hexane solution to the unsaponifiable residue, and after 5 minutes determine the absorbance. The difference between the first and the second absorbances is not less than 0.125.

Color Reagent—Prepare two stock solutions as follows.

Solution A—Empty, without weighing, the entire contents of a previously unopened 113-g bottle of dry, crystalline antimony trichloride into a flask containing about 400 ml of *Ethylene Dichloride*. Add about 2 g of anhydrous alumina, mix, and filter through filter paper into a clear-glass, glass-stoppered container calibrated at 500 ml. Add *Ethylene Dichloride* to make 500 ml, and mix: the absorbance of the solution, measured in a 2-cm cell, at 500 nm, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank, does not exceed 0.070.

Solution B—Mix, under a hood, 100 ml of acetyl chloride and 400 ml of *Ethylene Dichloride*.

Mix 45 ml of *Solution A* and 5 ml of *Solution B* to obtain the *Color Reagent*. Store in a tight container, and use within 7 days, but discard any reagent in which a color develops.

Chromatographic Tubes—

First Tube—Arrange for descending column chromatography (see page 865) a tube 2.5 cm in inside diameter, about 25 cm in length, and constricted to 8 mm in diameter for a distance of 5 cm at the lower end, by inserting at the point of constriction a coarse-porosity, sintered-glass disk or a small plug of glass wool. The constricted portion may be fitted with an inert, plastic stopcock.

Second Tube—Select a tube that is made up of three sections: (1) a flared top section, 18 mm in inside diameter and approximately 14 cm in length; (2) a middle section, 6 mm in inside diameter and approximately 25 cm in length; and (3) a tapered, constricted lower exit tube approximately 5 cm in length. Insert a small plug of glass wool in the upper 1-cm portion of the constricted section.

Chromatographic Columns—

First Column—To about 125 ml of isooctane contained in a screw-cap, wide-mouth bottle add 25 g of chromatographic siliceous earth, and shake until a slurry is formed. Add, dropwise and with vigorous shaking, 10 ml of polyethylene glycol 600. Replace the bottle cover, and shake vigorously for 2 minutes. Pour about half of the resulting slurry into the chromatographic tube, and allow it to settle by gravity. Then apply gentle suction, and add the remainder of the slurry in small portions, packing each portion with a 20-mm disk plunger. When a solid surface has formed, remove the vacuum, and add about 2 ml of isooctane.

Second Column—Pack the midsection of the tube with 3 g of moderately coarse *Chromatographic Fuller's Earth* with the aid of gentle suction (about 125 mm of mercury).

Standard Preparation—Dissolve about 25 mg of USP Ergocalciferol Reference Standard, accurately weighed, in sufficient isooctane to make 100.0 ml. Store in a refrigerator.

On the day of assay, transfer 1.0 ml of the standard solution to a 50-ml volumetric flask, remove the solvent with a stream of nitrogen, dissolve the residue in and dilute to volume with *Ethylene Dichloride*, and mix.

Sample Preparation—Unless otherwise directed, accurately weigh or measure a portion of the sample to be assayed, equivalent to not less than 125 µg but preferably about 250 µg of ergocalciferol (10,000 USP Units). If little or no vitamin A is present in the sample, add about 1.5 mg (the equivalent of 5000 USP Units) of vitamin A to provide the needed pilot bands in the subsequent chromatography.

For capsules or tablets, reflux not less than 10 of them in 10 ml of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for 5 minutes longer.

Add 2 ml of *Cottonseed Oil*, and then add a volume of *Potassium Hydroxide Solution* representing 2.5 ml for each g of the total weight of the sample plus cottonseed oil, but not less than 15 ml. Add 50 ml of alcohol. Reflux vigorously on a steam bath for 20 minutes, or for 30 minutes for samples weighing more than 5 g. If oil globules are evident, indicating incomplete saponification, add 5 ml of *Potassium Hydroxide Solution* (but not exceeding a total of 100 ml), and heat again. Cool, and transfer the saponified mixture to a 500-ml separator, rinsing the saponification flask with a total of 50 ml of water and adding each rinsing to the separator. Add about 4.5 g of sodium sulfate decahydrate and 150 ml of *Solvent Hexane*. Shake vigorously for 2 minutes. When the aqueous layer has separated, transfer it to a second separator. Extract with two 50-ml portions of *Solvent Hexane*, combine the extracts, and discard the aqueous solution.

Wash the combined *Solvent Hexane* extracts with 50-ml portions of water until the last portion shows no pink color on the addition of phenolphthalein TS. Allow the washed extract to stand for 5 minutes, discard any water that separates, and transfer the extract to a 300-ml tall-form beaker containing about 5 g of anhydrous sodium sulfate. Stir for 2 min-

utes, and decant the solution into a 500-ml, tall-form beaker. Rinse the sodium sulfate with four 25-ml portions of *Solvent Hexane*, combining the rinsings with the original extract. Reduce the total volume to about 30 ml by evaporation on a steam bath, and transfer the concentrate to a small, round-bottom evaporation flask. Rinse the beaker with four 5-ml portions of *Solvent Hexane*, adding the rinsings to the flask. With the aid of vacuum in a water bath at a temperature not exceeding 40°, or with a stream of nitrogen at room temperature, remove the remaining solvent completely. Dissolve the residue in a small amount of *Solvent Hexane*, transfer to a 10-ml volumetric flask, dilute to volume with *Solvent Hexane*, and mix to obtain the *Sample Preparation*.

Procedure—

First Column Chromatography—Just as the 2 ml of isooctane disappears into the surface of the prepared *First Column*, transfer 2.0 ml of the *Sample Preparation* to the column. As the meniscus of the *Sample Preparation* reaches the column surface, add the first of three 2-ml portions of *Solvent Hexane*, adding each succeeding portion as the preceding portion disappears into the column. Continue adding *Solvent Hexane* in portions of 5 to 10 ml until 100 ml has been added. If necessary, adjust the flow rate to between 3 and 5 ml per minute, by application of gentle pressure at the top of the chromatographic tube.

Discard the first 20 ml of effluent, and collect the remainder. Examine the column under ultraviolet light at intervals during the chromatography, and stop the flow when the front of the fluorescent band representing vitamin A is about 5 mm from the bottom of the column. (The ultraviolet lamp should provide *weak* radiation in the 300-nm region. It is frequently necessary to use a narrow aperture or screen with commercial lamps to reduce the amount of radiation to the minimum required to visualize the vitamin A on the column.)

Transfer the eluate to a suitable evaporation flask, and remove the *Solvent Hexane* completely in vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature. Dissolve the residue in about 10 ml of *Solvent Hexane*.

Second Column Chromatography—Transfer the solvent hexane solution obtained as directed under *First Column Chromatography* to the *Second Column*. Rinse the evaporation flask with a total of 10 ml of *Solvent Hexane* in small portions, adding each portion to the *Second Column* and allowing it to flow through the column, and discard the effluent. When about 1 ml of the *Solvent Hexane* remains above the surface of the column, add 75 ml of benzene, and elute with the aid of gentle suction (about 125 mm of mercury), collecting the eluate. Evaporate the benzene in vacuum at a temperature not above 40°, or with a stream of nitrogen at room temperature.

Assay Preparation—Dissolve the residue obtained as directed under *Second Column Chromatography* in a small amount of *Ethylene Dichloride*, transfer to a 10-ml volumetric flask, dilute to volume with *Ethylene Dichloride*, and mix to obtain the *Assay Preparation*.

Color Development—To each of three suitable, matched colorimeter tubes about 2-cm in diameter, and designated *1*, *2*, and *3*, respectively, transfer 1.0 ml of the *Assay Preparation*. To tube *1* transfer 1.0 ml of the *Standard Preparation*, to tube *2*, 1.0 ml of *Ethylene Dichloride*, and to tube *3*, 1.0 ml of a mixture of equal volumes of acetic anhydride and *Ethylene Dichloride*. To each tube add quickly, and preferably from an automatic pipet, 5.0 ml of *Color Reagent*, and mix. Forty-five seconds, accurately timed, after the addition of the color reagent, determine the absorbances of the three solutions at 500 nm, with a suitable spectrophotometer, using *Ethylene Dichloride* as the blank. Similarly, 45 seconds after making the first reading on each solution, determine the absorbances of the solutions in tubes *2* and *3* at 550 nm, in a similar manner. Designate the absorbances as A^1_{500}, A^2_{500}, A^3_{500}, A^2_{550}, and A^3_{550}, respectively, in which the superscript indicates the number of the tube and the subscript the wavelength.

Calculation—Calculate the quantity, in µg, of vitamin D in the portion of the sample taken by the formula:

$$(Cs/C)(Au/As)$$

in which Cs is the concentration of vitamin D, in µg per ml, of the *Standard Preparation*, C is the concentration of the sample (as g, capsules, tablets, *etc.*) in each ml of the final solution, Au has the value of $[(A^2_{500} - A^2_{550}) - 0.67(A^3_{550} - A^3_{550})]$ determined from the absorbances observed on the solution from the *Assay Preparation*, and As has the value of $(A^1_{500} - A^3_{500})$ determined on the solution from the *Standard Preparation*.

VOLUMETRIC APPARATUS

Most of the volumetric apparatus available in the United States is calibrated at 20°, although the temperatures generally prevailing in laboratories more nearly approach 25°, which is the temperature specified generally for National Formulary tests and assays. This discrepancy is inconsequential provided the room temper-

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

THE NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC., Plaintiffs, - against - CASPER W. WEINBERGER, Secretary of Health, Education and Welfare, and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs, Defendants.	Index No. 73 Civ. 3448 AFFIDAVIT

STATE OF NEW YORK)
) SS.:
COUNTY OF NEW YORK)

ALLEN SKOLNICK, being duly sworn, deposes and says:

1. I am the Vice-President of plaintiff Solgar Co., Inc., which is a member of the National Nutritional Foods Association. I have previously submitted an affidavit to this court in connection with the instant case and I present this additional affidavit in connection with label copy and potencies of vitamin A & D products which our company was utilizing prior to the effective date of the regulations at issue in this case.

2. I have been advised that the Food and Drug Administration has submitted to this court a sample of a label for a 50,000 I.U. vitamin A product which in part was labeled "take

one daily or as directed by physician." I am told that on the basis of this label for vitamin A, the agency is trying to prove that our company intended the sale of vitamin A & D products as drugs.

3. I respectfully wish to advise the court that the particular label submitted by the government and indeed the very product which it represents was discontinued by our company approximately during the month of September, 1971. This was more than one year prior to even the original agency prescription proposal for vitamin A & D and some two years before it finally went into effect. I do not see how this out of date label and product has any relevance to this case.

4. I would moreover state that in any event, the labeling indicating possible direction of use by a physician was not in any way designed to promote these products as drugs. Our company does not sell drugs. Physicians can recommend products for nutritional purposes and in fact it is common knowledge that doctors recommend dietary supplements in order to provide insurance for proper daily intake of vitamins and minerals. Our products have been and continue to be sold almost exclusively to health food stores. Even the few drug stores which do carry our products do so only in a separate health food section or

department.

5. Of more immediate relevance, are the products and labels for products which we were using at the time these regulations were proposed and placed into effect. In general, we were selling products containing 25,000 I.U. of vitamin A and either 1,000, 2,000 or 2,500 I.U. of vitamin D. These were sold either as part of general dietary supplements, particular combinations of vitamins A & D separately, or vitamin A separately. Representative labels are annexed hereto and made a part of this affidavit.

6. I feel that the court should know that our sale of these levels of vitamins was due in large part to the nature of the public demand for these potencies. For example, our earlier sales of the 50,000 I.U. levels met with very little public acceptance. On the other hand, the 25,000 I.U. product for vitamin A was extremely popular and continued to be so until the very day that these regulations went into effect. During the few months prior to the effective date of the prescription limitations, our offices were literally swamped with requests from health food stores throughout the country, pleading for emergency stocks of the 25,000 I.U. products. We were told that customers were buying 10 to 20 bottles at a time of this

particular product in order to have them available, after these regulations went into effect. In fact, we sold every single one of these products in our stock to the extent that I can not even find one label of this individual vitamin A product at 25,000 I.U. which we used to sell. There is no question but that the consuming public regards these products as nutritional foods although the Food and Drug Administration might disagree. In any event our company sold these products exclusively for food use as dietary supplements. None of these labels contained the references to use "as directed by physician." If the court has any remaining doubt as to my company's intent in the sale of these products, I am willing to testify in full so that our "objective intent" can be fully established to the satisfaction of the court.

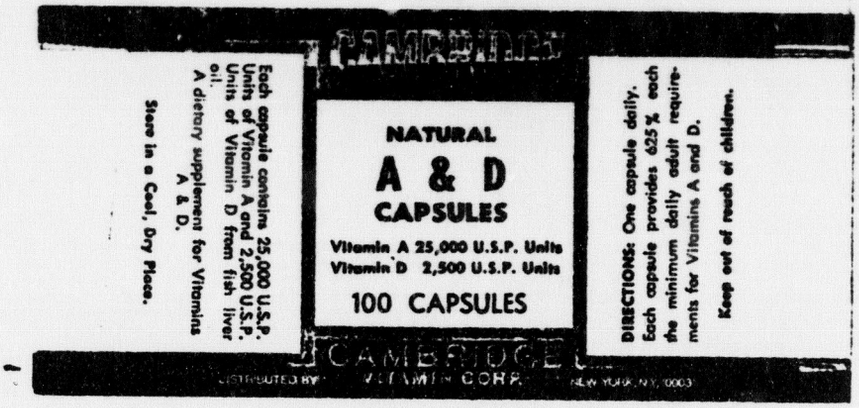
7. On the basis of my familiarity with the vitamin industry, I can state that the above described experience was not limited solely to my company. It was general knowledge in the industry that for example a 25,000 I.U. product for vitamin A was the particular potency in high demand among consumers particularly in health food stores. The industry met this public demand. The prescription limitations as discussed above, caused severe dislocations in the market structure for these products. I can state once again that in our many years

of experience, we have never received any complaint that one of our products had caused injury to any person. We are of course interested only in the sale of safe food products to the public. The sale of unsafe foods could only hurt our business reputation.

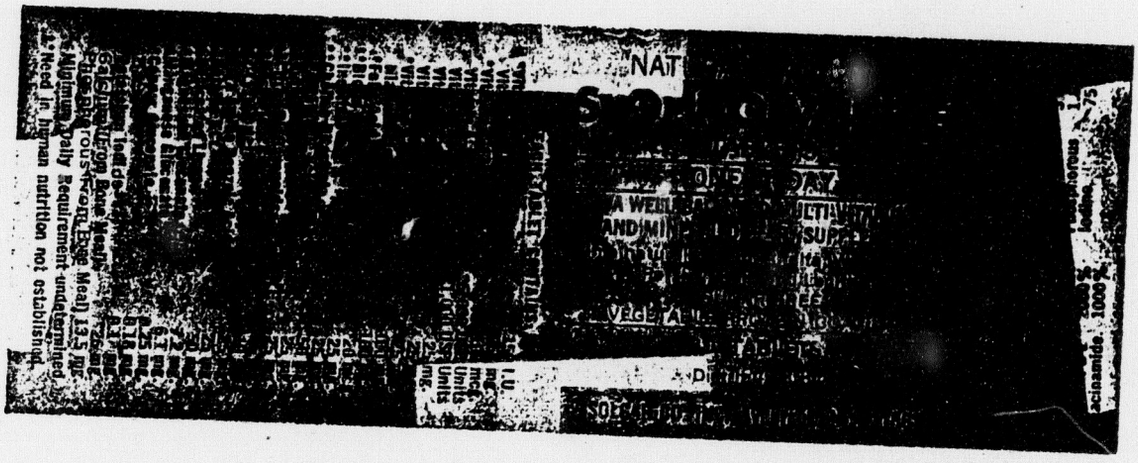
ALLEN SKOLNICK

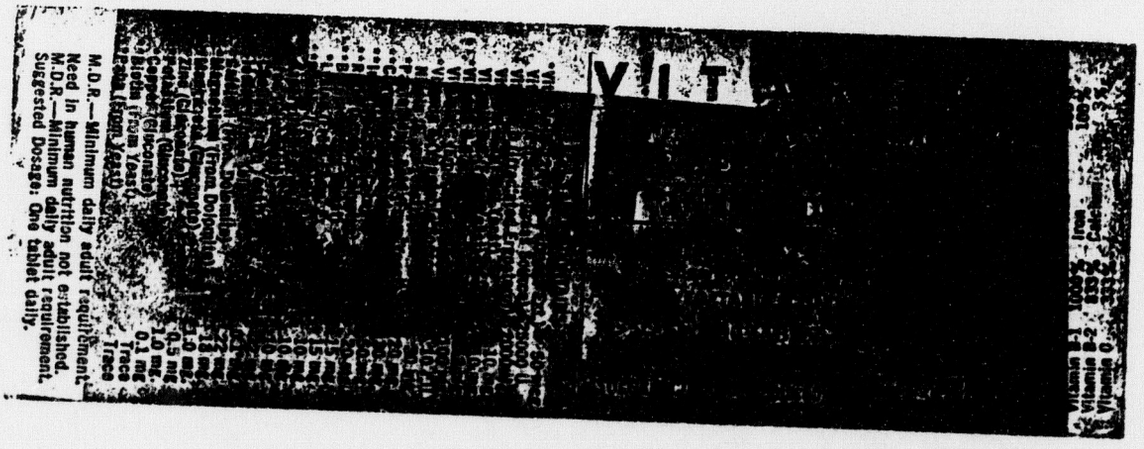
Sworn to before me this
28th day of May, 1975.

ROBERT ULLMAN
Notary Public, State of New York
No. 30-4051700
Qualified in Nassau County
Commission Expires March 30, 1975



The above is a product previously manufactured by Solgar for another company.





ADDITIONAL DOCUMENTS FURNISHED BY AGENCY

CORRESPONDENCE ANTEDATING PROPOSAL OF REGULATION

VITAMIN D

October 2, 1972

MEMORANDUM OF TELEPHONE COVERSATION

BETWEEN: Dr. R. C. B. Graham, Acting Director
Drug Advisory Board
Health Protection Branch
Food and Drug Directorate
Department of National Health and Welfare
355 River Road
Vanier City, Ottawa Ontario
Telephone: 613-992-4684

AND

Robert J. Rice, BD-30

SUBJECT: Pangamic Acid (Vitamin B_{15})

On this date Dr. Graham telephoned to answer our inquiry regarding the prescription drug status of vitamin D. Their requirement, finalized in May 1972 is that products recommending daily doses of vitamin D in excess of 1,000 IU should be prescription and that preparations recommending between 400 and 1,000 IU should bear a cautionary statement that the drug is for therapeutic use only.

In addition to discussing vitamin D, Dr. Graham requested information regarding pangamic acid. A Canadian physician has requested approval to use pangamic acid in human research in Canada. Reportedly, the Canadian physician says that pangamic acid is being used in the United States in research (investigational use) in the treatment of autistic and schizophrenic children. In addition, Dr. Graham indicated that he believes some research has been done regarding accelerated speech development with the use of pangamic acid.

Dr. Graham asked if we had any information regarding the investigational use of this drug in the United States and requested that if possible, could we telephone such information to Dr. Carol Scott within the next few days regarding any information. Her telephone is 613-993-1625. (We believe you can dial this through FTS (8-0-613-993-1625)).

(We note a long history of use of this drug in the treatment of mongolism. "U" Series of drugs, Ubiotica Corporation IND 1033, NDA 14-712 (not approved) is in part, pangamic acid.

Also, there have been other actions against pangamic acid promoted for conditions such as arthritis, various heart and circulatory problems and premature aging.)

Robert J. Rice

CC: BD-30/Reading BD-30 CA-228

RJRice:mlb:10/5/72

ge of Physicians & Surgeons of Columbia University | New York, N.Y. 10032
MENT OF NEUROLOGY
630 West 168th Street

456a

July 4, 1969

Jean D. Lockhart
au of Medicine
and Drug Administration
ington, D.C. 20204

Dr. Lockhart:

you will recall at the meeting of the Committee of Drugs of American Academy of Pediatrics in Buffalo, we discussed the ilability of vitamin A in large and potential toxic dosages r-the-counter. I have now accumulated a series of five patients have developed signs and symptoms of increased intracranial ssure following the long term ingestion of vitamin A prepara- ns. This was usually taken for the treatment of acne. Most the patients were referred to me as probable brain tumor ients and in some craniotomy was being considered.

m surprised that FDA permits the over-the-counter sale, not y of vitamin A in 25,000 to 50,000 unit doses but, above all a component in combinations of vitamins or multivitamin prep- tion in which the vitamin A component is at least in this high e range. In the near future, I plan to report the above cases the medical literature. However, I do want to bring this to e attention of the responsible authorities as soon as possible h the hope that this may prevent other cases of vitamin A icity.

Sincerely yours,

Arnold P. Gold, M.D.
Associate Professor of Clinical Neurology
(Pediatrics)

G:jg

...OF NEUROLOGY

4578

Tab C

630 West 168th Street

September 8, 1969

Vincent V. Karusaitis, M. D.
Medical Officer, Division of Case Review
Department of Health, Education, and Welfare
Consumer Protection and Environmental Health Service
Washington, D. C. 20204.

Dear Dr. Karusaitis:

I have recently returned from my vacation to find your letter of August 8, 1969, relative to Vitamin A toxicity. I will forward to you at some future time further data concerning the five cases of Vitamin A intoxication.

I do believe that multiple vitamin preparations containing 25,000 units of Vitamin A, such as are currently available over the counter, are potentially toxic, and that the sale of these preparations should be prohibited. The potential danger of vitamin intoxication is not recognized by the public as these are often considered innocuous compounds; for this reason the unsophisticated public must be protected. Furthermore there is absolutely no reason for multiple vitamin preparations to contain such an extensive quantity of Vitamin A.

If there are any further questions relative to this most important matter please feel free to contact me.

Sincerely,

Arnold P. Gold, M. D.
Associate Professor of
Clinical Neurology (Pediatrics)

APG:mb

458a

American Academy of Pediatrics

COMMITTEE ON DRUGS
Sumner J. Yaffe, M.D., Chairman
Children's Hospital, 219 Bryant St. • Buffalo, N.Y. 14222 • Area 716, 878-7503

March 2, 1972

Jean D. Lockhart, M.D.
Food and Drug Administration
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Dear Jean:

I am writing to follow up Committee activities with respect to Vitamin A. During the past several weeks, considerable interest in the abuse of Vitamin A has occurred again following the publication in the Winter issue of Family Safety of an article by Adelle Davis on Vitamin A.

In this article Miss Davis recommends very large doses of Vitamin A, in the order of at least 25,000 units or more a day. As you may remember, Dr. Simmons wrote to Dr. Gold on December 28, 1971, saying that the FDA had under consideration a statement of policy which will limit the maximum dosage of the vitamin which can be dispensed over the counter. Dr. Simmons went on to say that action was anticipated in the very near future.

I am writing to urge action in view of these more recent developments. If no action is taken on the part of the FDA, then I personally consider that the Committee on Drugs should bring this matter to the attention of Congress.

Would you kindly let me know as soon as possible what is being done and what in your opinion the Committee should do.

With best wishes,

Sumner J. Yaffe, M.D.
Chairman, Committee on Drugs

SJY/bws

TAB B

DEPARTMENT OF NEUROLOGY

630 West 168th Street

459a

September 8, 1969

Vincent V. Karusaitis, M. D.
Medical Officer, Division of Case Review
Department of Health, Education, and Welfare
Consumer Protection and Environmental Health Service
Washington, D. C. 20204.

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If there are any further questions relative to this most important matter please feel free to contact me.

Sincerely,

Arnold P. Gold, M. D.
Associate Professor of
Clinical Neurology (Pediatrics)

APG:mb

lege of Physicians & Surgeons of Columbia University | New York, N.Y. ...
ARTMENT OF NEUROLOGY 630 West 168th Street

460a

July 4, 1969

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reau of Medicine
od and Drug Administration
shington, D.C. 20204

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Sincerely yours,

Arnold P. Gold, M.D.
Associate Professor of Clinical Neurology
(Pediatrics)

PG:jg

461a File-Vit.A-D Reg.

BF-120

TO ALF

February 1, 1973

MEMORANDUM FOR THE FILE

Subject: Proposed Statement of Policy for Vitamins A and D, 21 CFR Part 3, December 14, 1972 (37 F.R. 26618)

On February 1, 1973, I received a copy of Attorney William R. Pendergast's letter of January 26, 1973, addressed to the Hearing Clerk, requesting that the time for filing comments on this proposal be extended to March 13, 1973.

After a discussion with Assistant General Counsel Peter Barton Hutt, I telephoned Mr. Pendergast and told him that there would be no formal time extension as he requested, but that we would consider any comments received on behalf of his client, Vitaminerals, Inc., Glendale, California, by March 13, 1973. Mr. Pendergast thanked me for this information.

Sam D. Fine

Sam D. Fine

cc: OC-1 OC-2 CC-1 CC-2 BD-1 BF-1
BD-30 BF-120 CC-20(Hearing Clerk) GC-1
CM-1

SDFine:eh 2/1/73

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1107 GRATIOT AVE.
GINAW, MICH. 48602

CO-PRESIDENT
JAMES B. GILLESPIE, M.D.
TENNIS COURT, N.W.
LA LUZ, ALBUQUERQUE, N.M. 87120

ECUTIVE DIRECTOR AND
EASURER
OBERT G. FRAZIER, M.D.

CRETARY
STANLEY L. HARRISON, M.D.

462a

American Academy of Pediatrics

1801 HINMAN AVENUE • EVANSTON, ILLINOIS 60204
EVANSTON (312) 869-4255 CHICAGO (312) 273-3546

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RIO DE JANEIRO, BRASIL
ULADISLAO LOZANO ESPARRA, M.D.
LIMA, PERU

February 15, 1973

Miss Beryl McCullar, Hearing Clerk
Department of Health, Education
and Welfare
Room 6-62
5600 Fishers Lane
Rockville, Maryland 20852

Dear Miss McCullar:

The Committee on Nutrition of the American Academy of Pediatrics, which has been active in nutritional matter for over 15 years, wishes to comment on the proposed regulations concerning Vitamin A & D which appeared in the Federal Register, Vol. 37, No. 241, December 14, 1972, pages 26618-26620.

The Committee on Nutrition recommends that Vitamin D in amounts up to 1000 I..U. be allowed without prescription in foods for special dietary use for specific medical problems - in this instance foods, designed for dietary management of subjects with poor Vitamin D absorption and steatorrhea or fat malabsorption.

Considerable evidence exists that there is Vitamin D deficiency leading to osteomalacia associated with steatorrhea. Providing Vitamin D in amounts up to 1000 I.U. for daily consumption in foods designed for patients with steatorrhea will provide some protection from Vitamin D deficiency and entails no risk of Vitamin D excess. This exception is requested only for special foods and not for vitamin and mineral supplements because the latter may be used in excess, whereas the foods cannot be taken in great excess.

This exception will permit continued use of established recommended dietary regimens for steatorrhea. Your consideration of this proposal will be appreciated.

Very sincerely yours,

Malcolm A. Holliday

Malcolm A. Holliday, M.D.
Chairman, Committee on Nutrition -
American Academy of Pediatrics

MAH:vs

MEMORANDUM OF TELEPHONE CONVERSATION

March 5, 1973

BETWEEN: Mr. Roger Barber
Assistant, Senator Metcalf's Office
and
Dr. Ogden C. Johnson

Information was requested concerning the regulations that would restrict the sale of vitamin A. A constituent of the Senator had called saying that the Food and Drug Administration would make it impossible to obtain any form of vitamin A other than with a prescription.

Dr. Johnson outlined the regulation that would control the sale of vitamins A and D, pointing out the products up to 10,000 I.U. per dose for vitamin A would be available as dietary supplements and, in some cases, over-the-counter drugs. It was further pointed out that the reason for the restriction was a possible health hazard. Requests from the American Academy of Pediatrics and the American Medical Association had initiated the action. In addition, the regulation was identical to that developed by the Canadian Food and Drug Directorate. Mr. Barker said that the information answered the inquiry and that, if he had any further data, he would call again.

Ogden C. Johnson, Ph.D.
Director
Division of Nutrition

cc: CL (Mr. Braunig)

PRESS RELEASE CHECK LIST

464a

SUBJECT: Vitamins A and D — RAM D.

PREPARED BY: E. R. Nida DATE: 11-30 PHONE: 33285

NOTE: WRITER RESPONSIBLE FOR APPROPRIATE PROGRAM PRE-CLEARANCE

CLEARED BY	OK	OK WITH CHANGE NOTED	DATE
WALDEN	✓	[illegible]	11 30
FINE (all Register items)	✓	[illegible]	12-1-72
GARDNER		Gardner	12-1
COMMISSIONER		[illegible]	

Final reviewer please call X-34177 for forwarding to DHEW

After clearance and BEFORE publication, notification given by writer to:

OFFICE OF LEGISLATIVE SERVICES: _____ date

ACFC (Mr. Hile) _____ date

OFFICE OF CONSUMER SERVICES: _____ date

STATE SERVICES (Mr. Kilpatrick) _____ date

NOTE: Associate Commissioner for Compliance to be contacted by writer immediately after DHEW clearance on all releases involving Federal Register action.

NEWS RELEASE

FOOD AND DRUG

Edward R. Nida: 301 443-3285
Home Phone: 301 365-4574

)3-

VITAMIN A and D PRODUCTS

FOR RELEASE:

The Food and Drug Administration today acted to limit the strength of Vitamin A and D products available for self-treatment without a prescription.

FDA's objective is to establish safe amounts of vitamins that can be effective as dietary supplements for use by consumers. Based on current scientific knowledge the Agency is proposing daily limits of 10,000 International Units (I.U.) for vitamin A and 400 I.U. for vitamin D. These figures are within the recommended daily dosages established by the Food and Nutrition Board, National Academy of Sciences - National Research Council.

The principal effect of the proposed regulations will be to have makers of multivitamins revise their formulas. Many multivitamin products are presently below the limits proposed for vitamins A and D. High-doseage vitamin products prescribed by physicians for specific patients will be unaffected.

Both vitamins are recognized as necessary to good human nutrition. However, excess amounts can be dangerous to both adults and children.

-MORE-

Reports of misuse of large doses of both vitamins A and D have prompted medical groups and FDA to seek limitations on them. Widespread promotion of both vitamins has resulted in excessive use for conditions such as acne, night blindness, and arthritis. Neither vitamin A nor D are proven effective for these conditions in well nourished people.

Excessive amounts of vitamin A taken over long periods can increase pressure within the human skull and brain tumors have been suspected in some cases. Large doses of this vitamin have also been shown to retard growth in children. Vitamin D has been known to retard mental and physical growth in children.

Interested persons may submit written comments within 60 days. Comments should be addressed to the Hearing clerk, Department of Health Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Maryland 20852.

####

Intracranial pressure -
Retardation of growth -

KELLOGG COMPANY
BATTLE CREEK, MICHIGAN 49016

July 30, 1973

Dr. Abel L. Robertson, Jr.
Professor
The Clinic Center
9500 Euclid Ave.
Cleveland, Ohio 44106

Dear Dr. Robertson:

This is in response to your recent letter regarding vitamin D toxicity.

We do not believe there is substantial evidence that vitamin D fortification at 400 I.U. per serving generally produces gross physiological toxicity symptoms. Most patients suffer from hypervitaminosis D have been given pharmacological doses of vitamin D (ranging from 12,000 - 500,000 I.U. vitamin D) for the treatment of hypoparathyroidism.[1] As with most any substance, if it is fed at high enough levels for a prolonged period of time, some physiological defects may be demonstrated. The toxic levels have usually been regarded as not less than about 50,000 USP units per day taken for a considerable period of time.[2]

In the 1969 White House Conference on Food, Nutrition and Health, Panel III - 1[3]recommended that "Steps should be taken to prevent nutrient deficiencies from the decline in the consumption of milk. The panel is concerned over the declining consumption of milk. Milk and dairy products supply about 75 percent of the calcium and 40 percent of the riboflavin in our national diet. This decline in the consumption of milk can materially affect the supplies of calcium, riboflavin, protein, and vitamins A and D in our diets."

We believe that our cereals contribute a significant amount of vitamin D to the consumer who otherwise would receive inadequate amounts.

---

[1]DeLuca, H.F., and J.W. Suttie, The Fat-Soluble Vitamins, 1969.

[2]Scott, H.T., Vitamin D in Nutrition, Wisconsin Alumni Research Foundation.

[3]White House Conference on Food, Nutrition and Health. Final Report, 1969.

Dr. Abel L. Robertson, Jr. July 30, 1973

It is reasonable to expect a recurrence of vitamin-D-deficiency symptoms if foods other than milk are not allowed to be fortified with vitamin D.

The RDA and U.S. RDA for children and adults has been established at 400 I.U. by the National Research Council and the Food and Drug Administration. In addition, this level has been set many times below that level which is generally considered toxic.

Many nutritionists recognize that there is a necessity for adding vitamin D to our food supply. This position was expressed by a well-known nutritionist in a recent column when he stated.[4]

> "Vitamin D is one vitamin which, in winter months, is not provided by an ordinary 'well-balanced' diet. Rickets is not the prevalent menace it once was, but it certainly would be if parents didn't give youngsters plenty of vitamin D enriched milk (with 400 International Units per quart), or a vitamin D supplement - - -"

---

[4]Dr. Jean Mayer, Chicago Tribune, November 30, 1972.

We hope this information is of interest to you, if you have any further questions, please contact us.

Sincerely,

KELLOGG COMPANY

William C. Morris, Ph.D.
Nutritionist

WCM:dks

TAB I

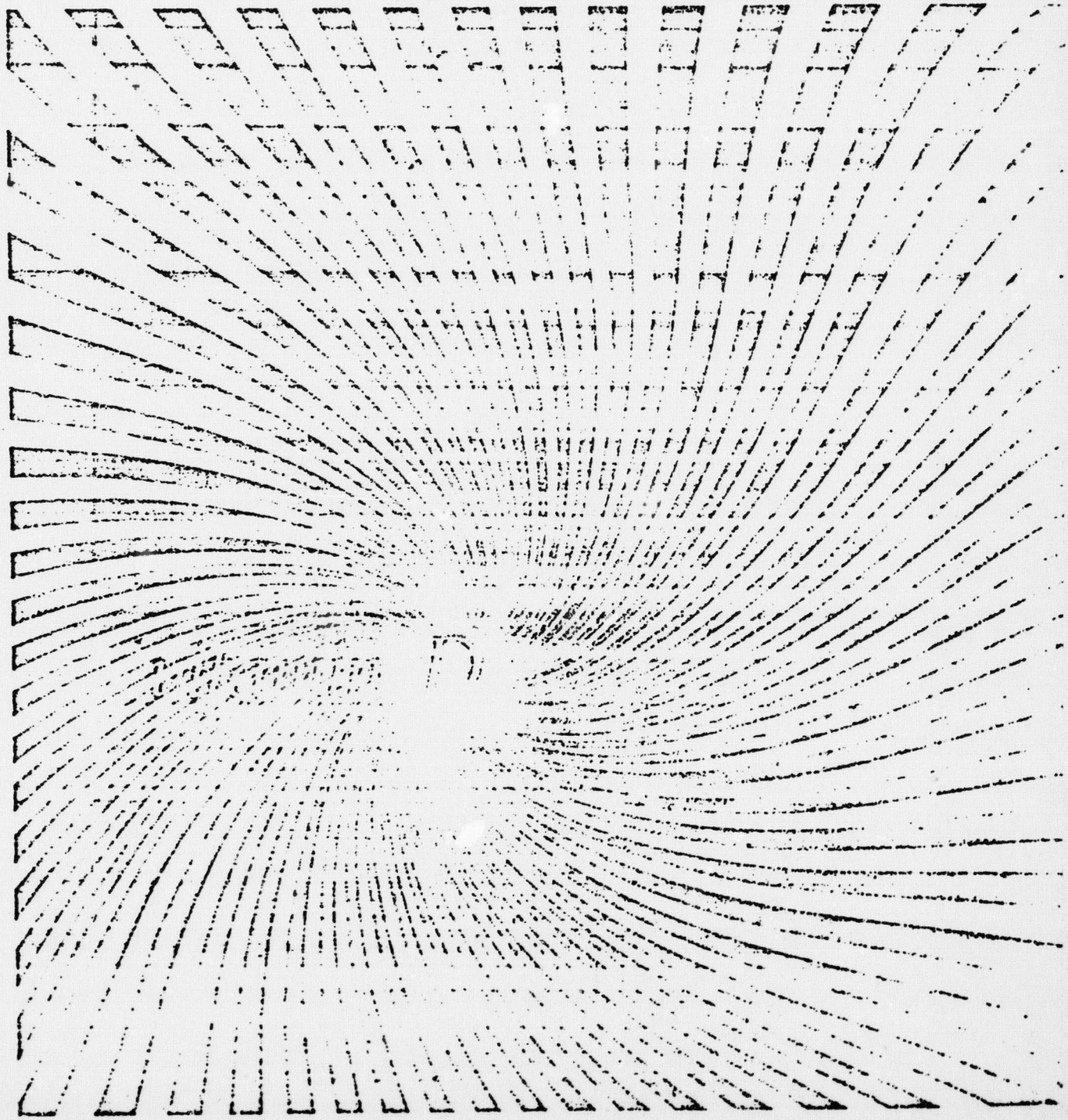
469a

19

VOLUME 3 • NUMBER 3 • MARCH

PUBLISHED BY THE HEALTH PROTECTION BRA

DEPARTMENT OF NATIONAL HEALTH AND WELFARE, OTTAW



Prescription Proposed

for high dosage

VITAMIN D

As a result of a careful review of the use of vitamin D, it has become obvious that while an adequate intake of vitamin D is essential there are certain definite risks associated with even modest intakes of the vitamin. The hazard is greatest in the high-potency products and in those that provide large amounts of vitamin D in the maximum recommended daily doses. With such products the danger is an excessively high daily intake of vitamin D. This has been implicated in the infantile hypercalcemia syndrome and can also lead to hypervitaminosis D.

Infantile Hypercalcemia Syndrome

The mild form of infantile hypercalcemia is the more common and may have an incidence of about 1 per 10,000 live births. It is characterized by hypercalcemia and a failure to thrive. The condition is reversible and has a good prognosis.

The severe form of infantile hypercalcemia has an estimated incidence of 1 per 120,000 live births in Canada. It is characterized by severe, permanent mental deficiency, supravalvular aortic stenosis, impaired renal function, an elfin appearance, hypercalcemia, and dense mineralization of certain bones. This form, which may have its inception in utero, has a bad prognosis.

Evidence that vitamin D may be involved in the development of both forms of infantile hypercalcemia has been provided by:

(a) epidemiological studies, particularly in the United Kingdom where there was an unusually high incidence of infantile hypercalcemia at a time when infants could have been receiving 4,000 I.U. per day.

(b) studies in affected children concerning blood and tissue levels, evidence of excessive intake, unusually slow elimination, or hypersensitivity to vitamin D, and

(c) studies of the vascular lesions produced in experimental animals by toxic doses of vitamin D administered during pregnancy, or to newborn or mature animals.

Although there is an appreciable amount of circumstantial evidence from all of these sources that vitamin D may play a significant role in the etiology and pathogenesis of infantile hypercalcemia, not all of the data are consistent, and the exact role of vitamin D has not yet been established for either form. Infantile hypercalcemia cannot be explained solely on the basis of excessive vitamin D intake because not all children who develop infantile hypercalcemia have had excessive vitamin D intakes.

and, similarly, not all children with excessive intakes develop the syndrome. It has been suggested that patients with infantile hypercalcemia, or their mothers, or both, may be hypersensitive to vitamin D or may have some disorder of vitamin D, or related, metabolism. Recent advances in the field of vitamin D metabolism may lead to the solution of the problem.

The problems presented by excessive vitamin D intake, especially in children, have been of concern to various organizations and agencies such as the British Paediatric Association, the British Ministry of Health, and the American Academy of Pediatrics. To reduce the risk of excessive intakes of vitamin D and yet to ensure adequate intakes to prevent vitamin D deficiency in children and adults, the Committee of Nutrition of the American Academy of Pediatrics has repeatedly recommended:

(1) continuation of enrichment of all types of milk at a level of 400 I.U. per U.S. quart,

(2) discontinuation of vitamin D enrichment of all other foods, except infant formula products,

(3) assessment by the physician of the dietary intake of vitamin D before prescribing any specific vitamin D supplement for an individual patient,

(4) no preparation sold over the counter should provide more than 400 I.U. vitamin D in the amount of the product designated on the label as the recommended daily intake, and

(5) products providing amounts of vitamin D in excess of 400 I.U. in the recommended daily dosage be restricted to sale only by prescription.

If an unambiguous causal relationship is established between vitamin D intake and the severe form of the hypercalcemic syndrome, the Committee would favour labelling products containing vitamin D to warn of the potential toxicity of excessive doses and to advise seeking medical advice before administering more than the recommended daily dose.

Toxicity or Hypervitaminosis D

In terms of unit body weight, dosages of vitamin D of 1000-3000 I.U./kg/day for several weeks or months can be toxic in infants and in adults; however, there is a fairly wide range of susceptibility to the toxic actions of the vitamin. The signs of hypervitaminosis include hypercalcemia, anorexia, nausea, weight loss, polyuria, constipation, and reversible azotemia. If the hypercalcemia continues long enough, generalized vascular calcification, nephrocalcinosis, and irreversible fatal renal insufficiency can develop. On the basis of 1000-3000 I.U./kg/day, the toxic dose for an infant would be 10,000-30,000 I.U./day.

Recommended Daily Allowance for Vitamin D

The recommended total daily intake of vitamin D from all sources (endogenous, dietary, and supplementary) is 400 I.U. This applies to all age groups from infants to adults, including women during pregnancy and lactation.

Except for specific therapeutic purposes, there is no necessity to exceed this recommended daily allowance.

Therapeutic Doses of Vitamin D

Therapeutic doses of vitamin D usually range from 1000 to 4000 I.U. per day for rickets or osteomalacia and from 10,000 to 500,000 I.U. per day for vitamin D dependency, vitamin D-resistant rickets, or hypoparathyroidism. For these conditions, vitamin D is specific and multivitamin therapy is neither necessary nor desirable.

Dihydrotachysterol can also be used in the treatment of hypoparathyroidism.

Very high doses (100,000-500,000 I.U. per day) of vitamin D have been recommended for the treatment of certain skin diseases (for example, psoriasis, lupus vulgaris), certain skeletal conditions (for example, osteoporosis, delayed union of fractures, Paget's disease) and cervical tuberculous adenitis; however such uses are not justifiable.

Products on the Canadian Market

Over 900 Drug Notification Forms for products which contain vitamin D have been received by the Health Protection Branch.

Number of Products	Maximum Recommended Daily Dose
691	400 I.U. or less
118	500-1000 I.U.
93	1100-8000 I.U.
14	10,000 I.U. or more

The 691 products which do not provide more than 400 I.U. vitamin D per day in the maximum recommended dose are considered to present no hazard. The 118 products which provide from 500-1000 I.U. per day in the maximum recommended doses provide up to 2.5 times the recommended daily allowance but probably present little or no risk, except to susceptible individuals. The 93 products which provide from 1100 to 8000 I.U. per day in the maximum recommended doses do present an appreciable risk both in infants and children and in women during pregnancy, especially in susceptible individuals. The 14 products which provide 10,000 I.U. or more per day in the maximum recommended doses represent a real hazard except when used for specific therapy under properly controlled conditions.

Proposed Regulations

A recommendation has been made to the Minister of National Health and Welfare that products for human use which contain vitamin D in daily doses exceeding 1000 I.U. should be sold only on a physician's prescription. It is further proposed that products containing between 400 and 1000 I.U. should carry a cautionary statement that the drug is for therapeutic use only.

A reasonable time will be given to manufacturers to comply with the labelling regulations.

The following measurable results can be expected:

(1) no products providing more than 1000 I.U. per day in the maximum recommended daily dosage will be available over the counter,

(2) no increase, even a decrease, in the incidence of rickets in Canada, and

(3) a decrease in the incidence of infantile hypercalcemia in Canada.

note to pharmacists

We are pleased to announce that copies of the [illegible] BULLETIN will be distributed to all licensed Pharmacists in Canada beginning with the April 1972 issue. A private mailing company is developing the mailing list for us. Presently, copies are being sent to all retail pharmacies. The distribution to these will be discontinued after the present issue.

TAB J

473a

ANALYSES OF 'STREET' DRUGS

Provision is made in the Narcotic Control and Food and Drug Regulations for a medical practitioner to accept samples of narcotic, controlled and restricted drugs from a person under his professional care and to pass those samples on to persons authorized to possess them for purposes of identification and analysis. This is intended to assist physicians in the management of patients who are misusing drugs.

The following persons recently have been authorized to possess these drugs. The names of other authorized persons were printed in the April 1971 and February 1972 issues of the EX BULLETIN.

Dr. K.R. Thornton
Royal Jubilee Hospital
Victoria B.C.

Mrs. Ann H. Gillespie
Royal Jubilee Hospital
Victoria, B.C.

Dr. R. Chong-Kit
Royal Columbian Hospital
Vancouver B.C. and the
Westminster Physicians Laboratory

Mrs. Kathleen I. Strausz
Toxicology Laboratory
Alberta Department of Health
Edmonton, Alberta

Dr. Donald J. Campbell
Division of Clinical Chemistry
Vancouver General Hospital
Vancouver, B.C.

Dr. Robert Hoare
The Cadham Public Health
Laboratory
Department of Health and Social
Development Brandon, Manitoba

Dr. Simone Radouco-Thomas
Centre Hospitalier de l'Université
Laval, Québec 10, Québec

M. Dominique Lamontagne
Laboratoire d'Expertises Inc.
Québec 10, Québec

Dr. Chong-Kit was previously authorized. He has changed his affiliation to the institutions listed above.

Mr. Thomas J. Martin, formerly of the York-Finch General Hospital, Downsview, Ont., is no longer authorized to possess narcotics and restricted drugs.

HIGH DOSAGE VITAMIN D NOW ON PRESCRIPTION

As a result of a careful review of the use of vitamin D, it has become obvious that while an adequate intake of vitamin D is essential there are certain definite risks associated with even modest intakes of the vitamin. The hazard is greatest in the high-potency products and in those that provide large amounts of vitamin D in the maximum recommended daily doses. With such products the danger is an excessively high daily intake of vitamin D. This has been implicated in the infantile hypercalcemia syndrome and can also lead to hypervitaminosis D.

A full account of the hazards of vitamin D overdosage and proposed regulations for vitamin D appeared in the March 1972 issue of EX BULLETIN. These regulations were printed in the Canada Gazette of May 24, 1972 and are now in effect. Products for human use which contain vitamin D in daily dosage exceeding 1000 I.U. may be sold only on a physician's prescription. Products containing between 400 and 1000 I.U. daily dosage must carry a cautionary statement that the drug is for therapeutic use only.

August 28, 1965

TAB J

Proposed Rule Making

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 3, 15, 16, 17, 18, 45, 121, 125]

VITAMIN D

Status as Special Dietary Food, Drug, Food Additive, and as Optional Ingredient in Standardized Foods

The need for vitamin D in human nutrition and the importance of maintaining a daily intake sufficient to protect infants and growing children from developing rickets is well established. It is widely recognized that a daily intake of 400 U.S.P. units of vitamin D is ample to prevent vitamin D deficiencies and is adequate for the supplementation of the diet of infants, children, and pregnant and lactating women. It is recognized also that vitamin D, when ingested daily in excessive amounts, is toxic. The question of possible excessive amount of vitamin D in the diet of the public was raised by Dr. Robert Cooke of Johns Hopkins University, Baltimore, Md. He expressed his concern that this may be an important factor in the development of infantile hypercalcemia. In doing so, he called attention to the fact that there are presently marketed a number of vitamin preparations labeled for special dietary use or with directions for use in self-medication as well as a number of foods with added vitamin D, which together may supply a substantially greater dosage of vitamin D than is necessary to accomplish its useful purpose.

In the interest of fully evaluating this problem, the Commissioner of Food and Drugs requested the Committee on Nutrition of the American Academy of Pediatrics and an ad hoc committee of the Council on Drugs and the Council on Foods and Nutrition of the American Medical Association to consider the possibility of hazard that may confront the American public in the consumption of currently available foods and vitamin supplements containing added vitamin D.

The Committee on Nutrition of the American Academy of Pediatrics has submitted a report containing the following recommendations:

1. The Committee wishes to reiterate the statement made in its published memorandum with respect to vitamin D fortification of foods other than milk or infant formula products: "* * * the present practice of enriching foods other than milk and infant formula products is not justified, and discontinuation of this practice is to be recommended."

2. The addition of vitamin D to fluid milk, evaporated milk or to special milk products and milk substitutes designed for consumption by infants is desirable and should continue. However, the vitamin D fortification should be carefully controlled so that in normal usage the total daily consumption will not be more than 400 units (i.e. 400 units/quart of fluid milk, or 400 units per reconstituted quart of formula products), which is the present practice in the United States. The addition of vitamin D to other foods may serve only to increase the intake by infants, children and pregnant women to levels beyond requirement.

3. Special purpose foods, designed to serve as the total daily source of nutrient or calories of infants, children or adults, may properly contain vitamin D. The vitamin should be added in an amount that does not exceed 400 units in the total daily intake.

4. At the present time, various vitamin preparations provide different amounts of vitamin D, some considerably in excess of 400 units in the recommended daily dosage. The Committee suggests that no preparations sold over the counter should provide more than 400 units of vitamin D in the amount of the product designated on the label as the recommended daily intake. Since it is the practice to dispense vitamin preparations designed for use by infants in liquid form, adjustment of intake from supplements to levels below 400 units/day remains feasible if consideration of total vitamin D available to the infant makes such reduction desirable. The Committee suggests that products containing amounts of vitamin D in excess of 400 units in the recommended daily dosage be restricted to sale only by prescription.

5. If in the future an unambiguous causal relation between vitamin D intake of the pregnant woman or the infant and the severe form of the hypercalcemic syndrome can be proved, the Committee would favor labeling of all vitamin products containing vitamin D so as to indicate potential toxicity if taken in excess of the recommended daily dosage. In addition, the user should be advised to seek medical advice before administering greater amounts of the product.

6. Before prescribing vitamin D supplements for any patient, the physician should assess the total intake of vitamin D from other sources, and unless high doses of vitamin D are required to treat specific disturbances of calcium and phosphorus metabolism, he should attempt to establish an intake of vitamin D of approximately 400 units per day from all sources. This applies for pregnant and lactating women as well as for infants and children. Normal adults living under ordinary conditions do not require supplementary vitamin D.

The joint ad hoc committee of the Council on Drugs and the Council on Foods and Nutrition of the American Medical Association has submitted a report with the following recommendations:

1. The addition of vitamin D to fluid, evaporated and dry whole milk, fluid skim milk, and nonfat dry milk should be permitted and encouraged but the quantity added should not exceed 400 USP units per quart of fluid or reconstituted milk.

2. The addition of vitamin D to milk substitutes and milk-based infant formulas which provide the sole or major source of calories should be encouraged. The vitamin D supplement should provide no more than 400 USP units in one quart of fluid when prepared for use.

3. Vitamin D supplementation of other food items should be prohibited.

4. Supplementary vitamin preparations available to the public for purchase without prescription should contain no more than 400 USP units of vitamin D in the suggested daily dose.

5. All vitamin preparations containing more than 400 USP units of vitamin D in suggested daily dosage should be prohibited from over-the-counter sale and should be available only by prescription.

6. Consumers should be advised that there is no advantage to the daily intake of more than 400 USP units of vitamin D and that the continued ingestion of amounts much in excess of that may be hazardous.

Copies of these reports are on file with the Hearing Clerk of the Department of Health, Education, and Welfare, and may be consulted by any interested person.

The Commissioner of Food and Drugs has reached the conclusion on the basis of these reports and on other relevant data and information available to him, including the abundant scientific evidence that an excessive intake of vitamin D is of no value, that it is prudent to issue a proposal which reflects the recommendations of these groups.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 403(j), 409(d), 502(f), 503(b)(4), 701 (a), (e); 52 Stat. 1046, 1043, 1051, 1052, 1055; 70 Stat. 919; 72 Stat. 1787; 21 U.S.C. 341, 343(j), 348(d), 352(f), 353(b)(4), 371 (a), (e)) and under the authority delegated to him by the Secretary of Health, Education, and Welfare (21 CFR 2.90) the Commissioner proposes to amend Title 21, Chapter I, of the Code of Federal Regulations in the following respects:

1. By adding to Part 3 the following new section:

§ 3.____ Vitamin D (vitamin D_2 (calciferol, ergocalciferol); vitamin D_3 (activated 7-dehydrocholesterol, cholecalciferol)).

(a) Vitamin D from any source, natural or synthetic, alone, or as a component of a food, for supplementing the human diet is regarded as a food additive subject to the provisions of section 409 of the Federal Food, Drug, and Cos-

Act and regulations promulgated thereunder.

(b) Any preparation containing more than 400 U.S.P. Units of vitamin D per dosage unit or any preparation supplying more than 400 U.S.P. Units per day when used in accordance with its directions for use is regarded as a drug that by reason of its toxicity or other potentiality for harmful effect, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer drugs. The label of any such article shall bear the statement "Caution: Federal law prohibits dispensing without prescription" and its labeling shall bear adequate information for its use by a practitioner licensed by law to administer it.

(c) Any drug containing vitamin D whose labeling bears directions for use in self-medication of vitamin D deficiency in recommended dosages greater than 400 U.S.P. Units per day will be regarded as misbranded within the meaning of sections 502 (a), (f), and (j) and 503(b)(4) of the act.

(d) Preparations supplying 400 or less U.S.P. Units of vitamin D represented or intended for use as drugs for the treatment of vitamin D deficiency by the lay public may be regarded as misbranded under sections 502 (a), (f), and (j) and 503(b) of the Federal Food, Drug, and Cosmetic Act, since adequate directions for safe and effective use for the self-treatment of vitamin D deficiency by the laity without medical supervision cannot be written.

2. By deleting from paragraph (b) of § 3.17 *Labeling of oleomargarine or margarine*, subparagraph 7, which is reserved, and by deleting from paragraph (d) of this section the phrase "vitamin D, or both".

3. By revoking paragraph (b) of § 15.10 *Enriched flour* * * *, which is reserved, and by changing the last sentence in the section to reflect the deletion.

4. By revoking paragraph (b) of § 15.60 *Enriched self-rising flour* * * *, which is reserved, and by changing the last sentence in the section to reflect the deletion.

5. By revoking paragraph (a)(2) of § 15.140 *Enriched farina* * * *, which is reserved; by deleting the next to the last sentence in paragraph (a), and by changing the last sentence of this paragraph to eliminate the reference to subparagraph (2).

6. By revoking paragraph (a)(2) of § 15.513 *Enriched corn meals* * * *, which is reserved, and by changing the third sentence in subparagraph (3) to reflect this deletion.

7. By revoking paragraph (a)(2) of § 15.514 *Enriched corn grits* * * *, which is reserved, and by changing the fourth sentence of subparagraph (3) to reflect the deletion.

8. By revoking paragraph (a)(2) of § 15.525 *Enriched rice* * * *, which is reserved, and by deleting the references to the revoked subparagraph (2) from paragraphs (a)(3), (b), and (c).

9. By revoking paragraph (a)(2) of § 16.9 *Enriched macaroni products* * * *, which is reserved, and by deleting the references to subparagraph (2) from paragraph (a)(5) and the last sentence of paragraph (a).

10. By revoking paragraph (a)(2) of § 16.10 *Enriched vermicelli products* * * *, which is reserved, and by deleting from paragraph (a)(5) and the last sentence of paragraph (a) the references to the revoked subparagraph.

11. By revoking paragraph (a)(2) of § 17.2 *Enriched bread and enriched rolls* * * *, which is reserved, and by deleting from the last sentence in paragraph (a) the reference to the revoked subparagraph.

12. By deleting the phrase "not less than" from paragraph (a)(2) of § 18.520 *Evaporated milk* * * *.

13. By deleting the parenthetical phrase "(with or without any accompanying vitamin D and with or without vitamin D concentrate)" from paragraph (a)(3)(iii) of § 45.1 *Oleomargarine, margarine* * * *.

14. By deleting the items "Vitamin D_2" and "Vitamin D_3" from the list in paragraph (d)(5) of § 121.101 *Substances that are generally recognized as safe.*

15. By adding to Subpart D of Part 121 the following new section:

§ 121.____ Vitamin D (Vitamin D_2, Vitamin D_3).

Vitamin D may be safely used in food in accordance with the following prescribed conditions:

(a) It is added to fluid milk, fluid nonfat milk, dry whole milk,[1] evaporated milk, concentrated milk, or infant-feeding formulations used in place of milk in an amount, in the case of fluid milk, fluid nonfat milk, dry whole milk, evaporated milk, or concentrated milk to provide 400 U.S.P. Units per quart of milk or reconstituted milk and, in the case of infant-feeding formulations used in place of milk in an amount to provide 400 U.S.P. Units per quart of such food as customarily or usually prepared for consumption; or

(b) It is a vitamin supplement or a component of a vitamin supplement that when ingested according to its labeled directions for use furnishes not more than 400 U.S.P. Units per day; and

(c) The food is labeled with a statement that vitamin D has been added; a statement of the number of U.S.P. Units of vitamin D in a specified quantity of the food; and in case it is an article covered by paragraph (b) of this section, it bears a label statement warning that unless prescribed by a physician the article should not be used to supplement the diet in excess of 400 U.S.P. Units per day from all sources.

16. By deleting the last sentence of paragraph (a)(1) of § 125.3 *Label statements relating to vitamins* and by deleting the last sentence of § 125.5 starting with the words, "The provisions of paragraph (c) * * *."

Any interested person may, within 60 days from the date of publication of this notice in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue SW., Washington, D.C., 20201, written comments, preferably in quintuplicate, on this proposal. Comments may be accompanied by a memorandum or brief in support thereof.

Dated: August 24, 1965.

GEO. P. LARRICK,
Commissioner of Food and Drugs.

[F.R. Doc. 65-9124; Filed, Aug. 27, 1965; 8:45 a.m.]

[1] Nonfat dry milk not included due to its statutory definition (Public Law 78-244, 58 Stat. 108, 70 Stat. 486; 21 U.S.C. 321(c)).

DEPARTMENT OF THE INTERIOR

National Park Service

[36 CFR Part 21]

HOT SPRINGS NATIONAL PARK, ARK.

Examining Board for Technicians

Basis and purpose. Notice is hereby given that pursuant to authority issued under section 3, 20 Stat. 258, as amended, section 3, 26 Stat. 843, as amended, sections 1–3, 39 Stat. 535, as amended, section 1, 41 Stat. 918, as amended, sections 1, 2, 67 Stat. 495, 496; 16 U.S.C. 1, 1b, 1c, 2, 3, 361, 363, 369, it is proposed to amend 36 CFR 21.15 as set forth below. The purpose of this amendment is to include two current managers of bathhouses as members of the Examining Board for Technicians and to increase the number of members required for a quorum. The bathhouse managers are the immediate supervisors of all technicians employed in the bathhouses, and the views and assistance of these managers would be of assistance to the Board in all matters concerning the technicians.

It is the policy of the Department of the Interior whenever practicable, to afford the public an opportunity to participate in the rulemaking process. Accordingly, interested persons may submit written comments, suggestions, or objections with respect to the proposed amendment to the Director, National Park Service, Washington, D.C., 20240, within 30 days of the date of publication of this notice in the FEDERAL REGISTER.

Section 21.15 is amended by adding subparagraph (6) of paragraph (a) and revising paragraph (c) to read as follows:

§ 21.15 Examining Board for Technicians.

(a) * * *

(6) Two persons who are currently engaged in managing bathhouses operating under contract with the Department of the Interior in Hot Springs.

* * * * *

(c) Six members present shall constitute a quorum. Any member undergoing disciplinary action or in suspension from duty shall not remain a member of the Board.

* * * * *

CLARENCE F. PAUTZKE,
Deputy Assistant Secretary of the Interior.

AUGUST 23, 1965.

[F.R. Doc. 65-9157; Filed, Aug. 27, 1965; 8:47 a.m.]

(Reprinted from Federal Register of Dec. 14, 1972, p. 26618)
* Correction published in F.R. 1/4/73; 38 F.R. 799

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

VITAMIN A AND VITAMIN D

Proposed Statement of Policy

Large doses of vitamin A and/or vitamin D ingested over long periods of time can cause adverse effects, some of which are serious. Vitamins A and D are fat-soluble and excess quantities accumulate in fatty tissue. The acute and chronic toxicity of these vitamins is documented extensively in the medical literature. Vitamin A is available over the counter in dosage levels up to 10 times the recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council (NAS–NRC), and vitamin D is available up to 60 times the RDA. The availability without prescription of these vitamins in high dosage levels contributes significantly to their misuse and the occurrence of serious adverse effects.

In view of the toxicity of excessive quantities of these vitamins, it is of concern to the Food and Drug Administration and medical authorities that there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders. In its "Newsletter" of June 1, 1972 (Vol. 23, No. 9), the American Academy of Pediatrics (AAP) comments on the critical dangers of use of high doses of vitamin A that have been recommended in the lay press, on radio, and on television. For example, the layman is being advised that he would profit from taking 25,000 international units (IU) of vitamin A with 2,500 IU of vitamin D, or twice these amounts, daily.

The AAP Committees on Drugs and on Nutrition published a joint committee statement entitled "The Use and Abuse of Vitamin A" in the journal "Pediatrics," Volume 48, Number 4, October 1971, warning physicians regarding vitamin A toxicity. This article states "Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through easy availability of high potency vitamin preparations without prescription and by the overzealous parents who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods." The AAP Committee on Drugs specifically has urged the Food and Drug Administration to limit the potency of vitamin A preparations available over the counter.

There exists considerable information in the literature regarding these vitamins and their toxicity. A listing of a number of pertinent articles, many of them recent, regarding these vitamins has been placed on file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, Md. 20852 for public view.

The highlights regarding toxicity of vitamins A and D and the rationale for limiting over-the-counter availability of these vitamins are as follows:

VITAMIN A

Adverse effects which result from excess intake of vitamin A include anorexia, growth retardation in children, drying and cracking of the skin, hepatosplenomegaly, increase intracranial pressure, alopecia, migratory arthralgia, bone pain, hypomenorrhea, irritability, and headache. Doses of 50,000 IU in adults and 20,000 IU in infants on a daily basis over long periods are known to produce toxicity. At present vitamin A is available over the counter in dosage levels as high as 50,000 IU per dosage unit. In recent years, some physicians and laymen have used large doses of vitamin A in the treatment of acne, although such therapy has not been shown to be safe and effective. Vitamin A in excessive dosages is used over long periods of time for this indication. Adverse effects, particularly increased intracranial pressure which may mimic a brain tumor, have been observed in children and young adults who are receiving vitamin A therapy for the treatment of acne. Reports of such effects have been published in the medical literature.

The position of the AAP on the matter is clear, as cited above.

In the United States, the Food and Nutrition Board, NAS/NRC, is the recognized authority for determining vitamin and other nutritional requirements for the human. The recommended daily dietary allowances (RDA) of the Food and Nutrition Board for vitamin A are 1,500 IU for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for older children and adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

Based on the above considerations, it is the opinion of the Food and Drug Administration and medical experts that preparations containing vitamin A in excess of 10,000 IU per dosage unit shall be dispensed only by prescription and that for any vitamin A preparation intended for distribution as a dietary supplement or as an over-the-counter drug, the recommended daily dosage shall not exceed 10,000 IU vitamin A.

VITAMIN D

There are marked differences in tolerances to Vitamin D in humans when quantities in excess of normal requirements are ingested over prolonged periods. There are significant numbers of individuals who are hyperreactive to excess vitamin D. Generally, the margin of safety between nutritional requirements and toxic levels is small for vitamin D. The margin is particularly small in those individuals who are hyperreactive.

In infants, children and adults, excessive ingestion of vitamin D results in hypervitaminosis D characterized by anorexia, nausea, weakness, weight loss, polyuria, constipation, vague aches, stiffness, generalized vascular, soft tissue and premature epiphyseal calcification, nephrocalcinosis, hypertension, anemia, hypercalcemia, acidosis, irreversible renal failure and death.

Daily ingestion by infants of doses between 1,000 and 2,000 IU has produced hypervitaminosis D, usually manifested as the infantile hypercalcemia syndrome. There is good evidence suggesting that the supravalvular aortic stenosis syndrome with hypercalcemia in infants and children may result from excess intakes of vitamin D by the infant and/or by the mother during pregnancy. This latter syndrome may have a tragic outcome with severe aortic stenosis, mental and physical retardation, elfin facies, renal failure and death.

The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin D for all age groups for which the vitamin is required is 400 IU. Although a daily intake of 400 IU of vitamin D is sufficient to prevent vitamin D deficiencies, preparations are available over the counter in dosage levels up to 25,000 IU per dosage unit. Excessive dosages of vitamin D have also been promoted in the lay press as noted above.

Based on the toxicity of vitamin D, the possibility of severe irreversible adverse effects in some instances, and the narrow margin of safety, it is the consensus of medical experts and the Food and Drug Administration that preparations containing vitamin D in excess of 400 IU per dosage unit shall be dispensed only by prescription and that the recommended daily dosage of any vitamin D preparation marketed as a special dietary food or as an over-the-counter drug shall not exceed 400 IU.

Therefore, because of the toxicity of vitamins A and D, their continued promotion in high doses to the lay person, and the continuing reports of adverse effects attributable to excessive intake of these vitamins, the FDA concludes it is in the interest of consumer safety to take the action herein described.

All vitamins are included among the over-the-counter drugs to be reviewed by an OTC Drug Advisory Review Panel, under the procedures established in the FEDERAL REGISTER on May 11, 1972 (37 F.R. 9464). Safety and effectiveness and more general questions related to adequate labeling of vitamin preparations marketed as OTC drugs will be considered by that panel, as well as the differences between foods for special dietary use, OTC drugs, and prescription drugs as they relate to vitamins. The Food and Drug Administration will publish, in the near future, new regulations governing dietary supplements of vitamins and minerals. Until such time as the OTC Drug Advisory Review Panel has completed its review and the new regulations for dietary supplements of vitamins and minerals are in effect, the Food and Drug Administration will not object to the inclusion in vitamin products marketed as foods for special dietary use or as OTC drugs of vitamin D at levels not exceeding 400 IU per dosage unit or 10,000 IU of vitamin A per dosage unit and with the recommended daily dosage not exceeding 400 IU of vitamin D or 10,000 IU of vitamin A.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502 (a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352 (a), (f), and (j), 353 (b), 371(a)) and under authority delegated to him (21 CFR 2.120), the Commissioner of Food and Drugs proposes to amend Part 3 by adding the following new sections:

§ 3.— Vitamin A preparations for oral use as drugs.

(a) Vitamin A is clearly known to be an essential nutrient for humans. Large doses of vitamin A can cause adverse effects, some of which are serious. The toxicity of vitamin A is well documented in the medical literature. The recommended daily dietary allowance (RDA) of the Food and Nutrition Board, National Academy of Sciences-National Research Council of vitamin A are: 1,500 international units (IU) for infants; between 2,000 and 3,500 IU for children 1 to 9; between 4,500 and 5,000 IU for adults; 6,000 IU during pregnancy, and 8,000 IU during lactation.

* (b) In view of the toxicity from the use of large doses of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(c) Preparations containing 10,000 or less I.U. of vitamin A per dosage unit will be regarded as misbranded if their recommended daily dosage exceeds 10,000 I.U.

(d) Vitamin A preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER). *

§ 3.— Vitamin D preparations for oral use as drugs.

(a) The importance of vitamin D in human nutrition is established. It is also widely recognized that vitamin D, when ingested daily in excessive amounts, is toxic. The recommended daily dietary allowance of vitamin D established by the Food and Nutrition Board, National Academy of Sciences-National Research Council for the prevention of vitamin D deficiency for all age and physiological groups for which the vitamin is required is 400 IU from all sources.

* (b) In view of the known toxicity and seriousness of the adverse effects that may be caused by excessive consumption of vitamin D, the Food and Drug Administration finds that in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 1.106(b)(3)(i) of this chapter, and especially appropriate warnings regarding vitamin D toxicity.

(c) Preparations containing 400 or less I.U. of vitamin D per dosage unit will be regarded as misbranded if their recommended daily dosage exceeds 400 I.U.

(d) Vitamin D preparations labeled or dispensed contrary to this statement will be subject to regulatory proceedings as of (60 days after day of final promulgation in the FEDERAL REGISTER). *

Interested persons may, within 60 days after publication thereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding these proposals. Comments may be accompanied by a memorandum or brief in support thereof. Comments received will be available for public inspection at the above office during regular business hours, Monday through Friday.

Dated: November 28, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

be integrated with the contributions or benefits under the Social Security Act. In such a case, the portion of the earned income (as defined in section 401(c)(2)) of such an individual which does not exceed the maximum amount which may be treated as self-employment income under section 1402(b)(1), and which is derived from the trade or business with respect to which the plan is established, shall be treated as "wages" under section 3121(a)(1) subject to the tax imposed by section 3111 (relating to the tax on employers) for purposes of applying the rules of paragraph (e)(2) of § 1.401–3, relating to the determination of whether a plan is properly integrated. However, if the plan covers an owner-employee, the rules relating to the integration of the plan with the contributions or benefits under the Social Security Act contained in paragraph (h) of § 1.401–12 apply.

PAR. 3. Paragraph (h)(3) of § 1.401–12 is amended to read as follows:

§ 1.401–12 Requirements for qualification of trusts and plans benefiting owner-employees.

* * * * * * *

(h) *Integration with social security.*

* * *

(3) If a plan covering an owner-employee satisfies the requirement of subparagraph (1) of this paragraph, and if the employer wishes to integrate such plan with the contributions or benefits under the Social Security Act, then—

(i) The employer contributions under the plan on behalf of any owner-employee shall be reduced by an amount determined by multiplying the earned income of such owner-employee which is derived from the trade or business with respect to which the plan is established and which does not exceed the maximum amount which may be treated as self-employment income under section 1402(b)(1), by the rate of tax imposed under section 1401(a); and

(ii) The employer contributions under the plan on behalf of any employee other than an owner-employee may be reduced by an amount not in excess of the amount determined by multiplying the employee's wages under section 3121(a)(1) by the rate of tax imposed under section 3111(a). For purposes of this subdivision, the earned income of a self-employed individual which is derived from the trade or business with respect to which the plan is established and which is treated as self-employment income under section 1402(b)(1), shall be treated as "wages" under section 3121(a)(1).

* * * * * * *

[F.R. Doc. 68–7974; Filed, July 5, 1968; 11:45 a.m.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 3, 15, 16, 17, 18, 45, 121, 125]

VITAMIN D

Withdrawal of Proposed Rulemaking

In the matter of amending Title 21, Chapter I, with reference to vitamin D intake:

A notice of proposed rulemaking in the above-identified matter was published in the FEDERAL REGISTER of August 28, 1965 (30 F.R. 11140), proposing a policy statement on vitamin D and changes in references to vitamin D in various food-standard, food-additive, and food-for-special-dietary-uses regulations.

In response to the proposal, over 90 comments were filed which with minor exceptions raised objections; however, the recommendations made in the comments were widely divergent.

In view of the time that has elapsed since the proposal was published and the comments were received, the Commissioner of Food and Drugs concludes that it should be withdrawn. Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 403(j), 409(d), 502(f), 503(b)(4), 701 (a), (e), 52 Stat. 1046, 1048, 1051–52, 1055, 70 Stat. 919, 72 Stat. 1787; 21 U.S.C. 341, 343(j), 348(d), 352(f), 353(b)(4), 371 (a), (e)) and under authority delegated to the Commissioner (21 CFR 2.120), the proposed rulemaking published in the FEDERAL REGISTER of August 28, 1965 (30 F.R. 11140–41), regarding vitamin D is hereby withdrawn.

This action is entirely separate from and independent of the orders published in the FEDERAL REGISTER of June 18, 1966 (31 F.R. 8521, 8524, 8525), and the subsequent proceedings concerning foods for special dietary uses and dietary supplements.

Dated: May 14, 1968.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

[F.R. Doc. 68–8039; Filed, July 5, 1968; 8:48 a.m.]

weight. There were no specific adverse effects. Dietary levels of 500 ppm, or less, of pimaricin were well tolerated by rats over a 2 year period. No significant hematological changes and no relevant gross or microscopic lesions were observed.

Dogs maintained on diets containing 125 ppm to 250 ppm of pimaricin for 2 years showed no deleterious effects.

DOSAGE AND ADMINISTRATION

One Pimafucin vaginal tablet 25 mg is inserted every night high into the vagina before going to sleep. Treatment should be started immediately after menstruation and be continued for 20 days. In persistent cases treatment should be continued through one or two cycles.

Scrupulous attention to personal hygiene is important in the prevention of reinfection; the male partner can also constitute a source of reinfection.

DOSAGE FORMS

Each buff-coloured vaginal insert contains: pimaricin 25 mg, benzalkonium chloride 1 mg with lactose and sufficient buffering agents to restore correct physiological conditions.

Boxes of 20 inserts with applicator.

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PRESCRIPTION REQUIRED FOR HIGH DOSAGE VITAMIN A

The beneficial effects of vitamin A are well recognized but the ingestion of excessive amounts can cause severe toxic effects. In recognition of this and after consultation with the Canadian Pediatric Society, FDD recommended (our position was outlined in the March 1971 issue of BULLETIN) that products for human use which contain vitamin A in daily doses exceeding 10,000 I.U. should be sold to the general public only on a physician's prescription. A regulation to this effect (subsection 2 below) was passed on May 25, 1971. The pertinent revised regulations are as follows:

D.04.011.(1) Subject to subsections (2) and (3), no person shall sell or advertise a drug that is represented as containing a vitamin if the largest recommended daily dosage of that drug shown on a label thereof would, if consumed by a person, result in the daily intake by such person of more than (a) in the case of vitamin A, 10,000 International Units.

(2) Where a drug referred to in paragraph (a) of subsection (1) carries the symbol Pr on the upper left quarter of the main panel of both the inner and outer labels, a person may sell the drug to

(a) the general public, if it is sold on prescription;
(b) a drug manufacturer;
(c) a practitioner;
(d) a wholesale druggist;
(e) a registered pharmacist;
(f) a hospital certified by the Department of National Health and Welfare;
(g) a Department of the Government of Canada or of a province, upon receipt of a written order signed by the Minister thereof or his duly authorized representative; or
(h) any other person, upon receipt of a written order signed by the Director.

(3) Subsection (1) does not apply to a drug

(a) that is prepared for parenteral use only; or
(b) that is required to be sold on prescription by Regulations made under the Act or the *Narcotic Control Act*.

A reasonable time will be given to manufacturers to comply with the labelling regulations.

PROPOSED FOR VITAMIN D

Although the beneficial effects of vitamin D are well recognized, the ingestion of excessive amounts can cause severe toxic effects. A recommendation has been made to the Minister of National Health and Welfare that products for human use which contain vitamin D in daily doses exceeding 1,000 I.U. should be sold only on a physician's prescription. It is further proposed that products containing vitamin D in daily doses between 400 and 1,000 I.U. should carry a cautionary statement that the drug is for therapeutic use only.

Further details will appear in a subsequent issue of BULLETIN.

NEWSLETTER
AMERICAN ACADEMY OF PEDIATRICS
1801 HINMAN AVENUE • EVANSTON, ILLINOIS 60204
Volume 23 Number 9 (NEXT PAGE) June 1, 1972

MENINGOCOCCAL POLYSACCHARIDE VACCINE RESULTS REPORTED

Spring Session Scientific Program Generates Large Attendance

The 1972 spring meeting in San Diego attracted one of the largest attendances for a spring session in the history of the Academy. Approximately 1,350 physicians attended the meeting. Total attendance reached 2,253.

The scientific program included presentations on the control of meningococcal meningitis, the current high level of venereal disease reported in the U.S., and the dangers of a therapeutic abortion in an ill-equipped or badly managed clinic.

Scientific papers were also presented on pediatric emergencies, current concepts in infectious diseases, and respiratory distress syndrome.

Meningococcal Meningitis

Lt. Cmdr. Thomas A. Hoffman, MC, USNR, U.S. Naval Hospital, San Diego, Calif., in his presentation stated that the use of a group c meningococcal polysaccharide vaccine at the U.S. Naval Training Center and the U.S. Marine Corps Recruit Depot in San Diego has lead to a significant reduction in reported cases of type c meningococcal meningitis.

Dr. Hoffman reported that in fiscal year 1970-71 a total of 209 cases of the type c disease was reported at the two bases. "The number of cases decreased abruptly after the vaccine program was instituted," Dr. Hoffman said. "Since last July, only sixteen cases have been reported." Dr. Hoffman further explained three of the 16 cases were caused by another strain of bacteria known as group y meningococci. "The vaccine was also effective in reducing the disease carrier rate and, apparently, the transmission of group c meningococci."

Dr. Hoffman said the vaccine was developed in 1969 at Walter Reed Army Institute of Research in Baltimore, Md., and was utilized on a trial basis the same year among military recruits at several bases. Routine use of the vaccine at the San Diego bases began last fall.

Venereal Disease

Elizabeth Barrett-Connor, M.D., assistant professor of epidemiology and medicine, San Diego School of Medicine, told the physicians in attendance that venereal disease is now epidemic in the United States with levels higher than they ever have been before in this country. Dr. Barrett-Connor further stressed that gonorrhea is occurring more prevalently in the younger age set, and that half of the patients with the recognized disease are 25 years old or younger.

Referring to a recent survey conducted at San Diego's University Hospital, Dr. Barrett-Connor indicated that according to the survey, only twenty percent of San Diego's pediatricians reported cases of venereal disease.

"It is highly unlikely," she stated, "that the other eighty percent did not have any cases to report." In view of the epidemic, Dr. Barrett-Connor told the audience it is not likely venereal disease is going to spare children or adolescents.

Therapeutic Abortion

Paul Bremer, M.D., clinical professor of obstetrics and gynecology at the University of California at San Diego School of Medicine, stated in his presentation on pregnancy, abortion, and free clinic that many pro-

Continued on Page 3

Pan American Congress To Meet in Argentina

The joint meeting of the tenth Pan American Congress, the third Latin American Congress and the second Argentinian Congress will be held November 5-10 in Cordoba, Argentina.

Scientific presentations on nutrition, gastroenterology, infectology, and enzymology will be presented in a comprehensive program of general sessions, round tables, and seminars planned for the joint meeting. Also, the Academy has arranged a special tour enabling physicians to visit Central and Latin American countries and pediatric facilities. A brochure on the tour has previously been mailed to the Academy membership.

Information

Registration applications and additional information about the Congresses may be obtained by writing Carlos A. Rezzonico, M.D., F.A.A.P., C. C. 141, Cordoba, Argentina. Information about the tours can be obtained by writing International Travel Service, Inc., 104 S. Michigan Ave., Chicago, Ill. 60603.

COMMITTEE STATEMENT 481a

Committee on Nutrition

MISUSE OF VITAMIN A

The use of high doses of vitamin A (25,000 to 50,000 units/day) has been recommended by Adelle Davis in the lay press,[1] on radio, and on television. Doses of vitamin A in this range can produce toxic effects in children, the most serious manifestation of which is increased intracranial pressure mimicking brain tumor.[2] Pediatricians should advise parents of this danger.* The recommended daily allowances of vitamin A are 1,500 units/day for infants, 2,000 to 3,500 units/day for children 1 to 10 years of age, and 4,500 to 5,000 units/day thereafter.[3] These quantities can be achieved by the ordinary diet. If a vitamin supplement is needed, the daily intake of vitamin A should not exceed the above levels

When a child with increased intracranial pressure is seen, the pediatrician should consider vitamin A intoxication in the differential diagnosis, the more so if the skin is dry and the hair sparse, and there is considerable irritability and anorexia.

The Nutrition Program, Center for Disease Control, Atlanta, Georgia 30333, or the Clinical Nutrition Laboratory, Laboratory Centre for Disease Control, Health Protection Branch, Tunney's Pasture, Ottawa, Canada, can be contacted for addresses of laboratories where blood determinations of vitamin A can be made.

*Excessive use of vitamin A in the treatment of acne is also hazardous.

COMMITTEE ON NUTRITION

L.J. Filer, M.D., Chairman
Malcolm A. Holliday, M.D., Interim Chairman
Lewis A. Barness, M.D.
Richard B. Goldbloom, M.D.
James C. Haworth, M.D.
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Charles F. Whitten, M.D.

Consultants
Joaquin Cravioto, M.D., M.P.H.
O.L. Kline, Ph.D.

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1972 JUNE MEETINGS OF ACADEMY NATIONAL COMMITTEES

2	Chapter Award Committee	Evanston, Ill.
2 -3	Third Party Payment Plans Committee	Evanston, Ill.
10 - 11	Committee on Purpose, Policy and Structure	Evanston, Ill.
12 - 13	Committee on Nutrition	Evanston, Ill.
15 - 16	Committee on Disaster-Emergency Medical Care	Evanston, Ill.
19-20-21	Committee on Drugs	Buffalo, N.Y.

Spring Session Cont'd.

grams established under the newly established individual states' abortion legislation have been ill-planned or conducted by groups serving their own aims rather than the needs of patients.

Stating he was not discussing the morality of therapeutic abortion, Dr. Brenner cited examples of abortion clinics in California and New York where massive numbers of abortions are performed with little or no follow-up examination or treatment. He stated that in California abortions are performed figuratively by the hundreds per day without adequate facilities to manage emergencies. He also cited the lack of a prerequisite for a history or a physical examination. Dr. Brenner called upon the medical profession to take stronger action in establishing efficient abortion programs directed toward accommodating patients within proper hospital settings.

Dr. Brenner stated that the abortion problem is just one of a series created by technological progress. The problem, he indicated, is related to many social problems -- abortion, contraception, sex education, hippies and runaways.

"Many of those runaways, those hippies, many of those bodies at the free clinic are mutilated spirits who have never received love nor have been wanted."

The physician's role in today's technological society, according to Dr. Brenner, is to become emotionally and physically involved in a changing society; to attempt to gaze into the future in order that the technological realities can be implemented intelligently into the society of the future; to provide adequate care for stressed individuals on their terms, and to act as an interlocutor within the family unit. Doctors should provide a public educational program which will eliminate the medical mysticism which separate the patient from the physician, Dr. Brenner concluded.

increase the diagnostic yield from standard studies without having to resort to esophagoscopy, fiberoptic gastroduodenoscopy, fiberoptic retrograde colonoscopy, abdominal vascular studies, or as a final resort, exploratory laparotomy.

The technics require little extra time, no sophisticated equipment, and are well worth the small extra effort in affording the radiologist the opportunity to report "there is" rather than "there may be."

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CASE REPORT

Increased Intracranial Pressure: Consequence of Hypervitaminosis A

LAURENCE A. GROSSMAN, MD,† *Nashville, Tenn*

Vitamin A intoxication resulting in intracranial hypertension and appropriate neurologic signs and symptoms previously has been reported in 6 adults. Gerber and associates,[1] in 1954, described a woman who had been taking high doses of vitamin A for one year, and then developed diplopia, headache, nausea and blurring of vision. She had blurred disk margins, a retinal hemorrhage and nystagmus. While under observation over a 7 year period, her choked disks progressed to optic atrophy, accompanied by slight dilation of the lateral ventricles. The vitamin A was continued, and she was treated by subtemporal decompression.

In 1958, Oliver and Havener[2] reported a 14 year old girl on large doses of vitamin A for acne vulgaris. After 10 months she developed papilledema and an increase in intracranial pressure without pleocytosis or elevation of protein in the cerebrospinal fluid. The papilledema disappeared after vitamin A was discontinued.

In 1960, 2 additional cases were described by Morrice and associates[3] with rather typical findings of pseudotumor cerebri; these were in 15 and 16 year old girls.

With the discontinuance of vitamin A the symptoms and physical findings disappeared.

Feldman and Schlezinger,[4] in 1970, reported 2 patients with benign intracranial hypertension associated with hypervitaminosis A, both 29 years of age. The papilledema, retinal hemorrhages, visual field defects and headache disappeared when vitamin A was discontinued.

Case Report. A 17 year old high school student was admitted with a history of one month's illness. The initial symptoms were vague aching pains and low-grade fever. There were pains in both legs anteriorly, which the football coach suggested might be "shin-splints." For 2 weeks he had had vomiting, weight loss and anorexia. Five days before admission he had blurring of vision and diplopia. The blurring persisted. He had had a 30 pound loss of weight in the 2 month period.

Physical examination disclosed a young male appearing chronically ill and quite weak. The skin was excoriated on the face, trunk, and upper extremities. The lips were dry and fissured, with some crusting. The neck was not obviously stiff, but there was a mildly positive Kernig. The pupils were moderately dilated, but reacted normally to light. A bilateral 6th nerve palsy was evident by weakness of the external rectus muscle, more pronounced on the left. There was horizontal diplopia. Both optic disks were swollen to a 2 diopter level, but the papilledema was not accompanied by hemorrhages. Small, shotty lymph nodes were palpable in the axillary, epitrochlear and inguinal areas. The lungs were clear. The heart was normal. There was no hepatosplenomegaly. The deep reflexes were active and equal. The plantar responses were equivocal, but there was no definite Babinski's reaction. Sensation was intact.

The additional information was then obtained that

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†From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

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Continued from page 916

for 10 months he had taken large doses of vitamin A, ranging from 300,000 to 400,000 units daily. He had also taken vitamin C and vitamin E, but in more modest amounts. His general health had been excellent throughout this time, and he had played high school football before the onset of the present illness.

Laboratory studies revealed that the PCV, Hgb, WBC count, differential count and urinalysis were normal. Chemical tests of liver function were normal. The chest film, skull films, and films of the lower extremities were normal. The EEG was mildly abnormal, as shown by diffuse slowing, thought to be secondary to increased intracranial pressure. The brain scan was normal.

Lumbar puncture revealed an opening pressure of 510 mm of water with normal dynamics. There were no cells. The spinal fluid protein was 15 mg/100 ml.

On Dec 18, 1971, 2 days after admission, the vitamin A level was 327 mcg/100 ml and the following day it was 294 mcg. The serum carotene was 56 mcg/100 ml.

He remained in the hospital one week. No medication was prescribed. His hospital course was uneventful, and the headaches rapidly cleared. Within a week the bilateral 6th nerve involvement was barely detectable. The papilledema persisted. One month later he was asymptomatic, with only minimal residual papilledema.

Comment. In infants, acute intoxication with vitamin A at times results from accidental overdose of vitamin drops. The effects of acute toxicity are drowsiness, vomiting, and bulging of the fontanelles from an increase in intracranial pressure. Evidence of chronic toxicity includes failure to gain weight, alopecia, coarseness of hair, hepatomegaly and bone pain. X-ray examination of the skeleton shows characteristic areas of periosteal new bone formation, particularly prominent in the shafts of the long bones.

Kane,[5] an arctic explorer, first suggested vitamin A intoxication as the cause of the vertigo and headache that occurs transiently following ingestion of polar bear liver, which was found to contain a high concentration of vitamin A. Much later, similar observations were observed in adults following the eating of shark liver, which also is rich in vitamin A.

The carotenemia, which is found when large amounts of vitamin A are consumed, is also seen when carotene-containing foods are eaten in excessive quantities. In such cases the blood plasma may contain high concentrations of this pigment and may impart a yellowish color to the skin, but not to the conjunctivas.

The symptoms which this patient presented, the papilledema and the 6th nerve palsy, all resulted from intracranial hypertension. Edema of the brain actually has been found on biopsy in such patients, with swelling of all cellular elements. The actual mechanism or etiology of the intracranial hypertension associated with hypervitaminosis A is not known. Many theories have been offered to explain this. The clinical picture is identical with that described as pseudotumor cerebri. Actually, many systemic illnesses have been described as leading to increased intracranial pressure with papilledema, and without evidence of intracranial mass lesions. These include hypoparathyroidism, infectious mononucleosis, tetracycline, lupus erythematosus, blood dyscrasias, sarcoidosis, certain psychotherapeutic drugs, etc. Hypervitaminosis A is another possible causative condition.

Summary. A 17 year old boy developed intracranial hypertension, papilledema, and bilateral 6th nerve palsy, as a result of vitamin A intoxication. The illness was self-limited. Discontinuance of the vitamin A resulted in clearing of the neurologic symptoms and signs. The clinical syndrome is identical with that of pseudotumor cerebri.

1816 Hayes St
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AMERICAN ACADEMY OF PEDIATRICS

JOINT COMMITTEE STATEMENT
COMMITTEES ON DRUGS AND ON NUTRITION

THE USE AND ABUSE OF VITAMIN A

VITAMIN A is an essential nutrient necessary for maintenance of normal epithelial tissue and for optimal growth.[1,2] Impaired dark-adaptation and night blindness are well known manifestations of vitamin A deficiency. Although vitamin A is present in many foods, it cannot be assumed that all individuals receive adequate amounts. Preliminary reports from the recent 10-state nutrition survey* show that a significant proportion of the population has a low intake of vitamin A and low plasma vitamin A levels. Thus it would appear important to improve the diet of a considerable segment of the population or provide a vitamin A supplement for them.

Vitamin A is found in food in carotenoids, which are converted to vitamin A in the intestine; or, it may be preformed, as in foods from animal sources (or in diet supplements). There is no danger of excessive intake of vitamin A when carotenoids are ingested.

The recommended daily allowances of vitamin A are: for infants and children up to age 12 years, from 1,500 to 4,500 I.U.; for adults, 5,000 I.U.; and for pregnant women 6,000 I.U.[3,4] Although diets of many individuals provide higher levels of vitamin A, there are no known advantages in exceeding these allowances in normal individuals.

Thus, for prophylactic use or as a safeguard against inadequate intake, there are properly formulated supplements available on the market, i.e., those that contain 1,500 to 4,000 I.U. for infants and children, 5,000 I.U. for adults, and 6,000 I.U. for pregnant women.

However, excessive intake of preformed vitamin A may result in serious and potentially toxic effects. The easy availability of vitamin A in large doses without prescription exposes individuals to the danger of severe clinical toxicity. Physicians should be aware of the circumstances in which vitamin A toxicity may occur and its clinical manifestation.

Doses of 25,000 I.U. or more of vitamin A, which are present in some vitamin preparations, should not be used, unless severe deficiency of vitamin A, documented by an abnormally low blood level, exists. These doses taken daily for an extended period of time pose a risk, particularly to the pregnant woman and fetus. Studies in pregnant animals have shown that large doses of vitamin A produce central nervous system anomalies with hydrocephalus, encephalocoele, and other teratological effects in the offspring.[5,6] Infants may develop a bulging fontanel or hydrocephalus when given about 10 times the recommended daily allowance of vitamin A for several weeks.[7-9] The older child or adult with hypervitaminosis A manifests pseudotumor cerebri, a syndrome that may simulate the presence of an intracranial neoplasm, with signs and symptoms of unlocalized increased intracranial pressure,[10-13] such as headache, nausea, vomiting, lethargy, tinnitus, and diplopia. Physical findings are usually limited to the eyes, with sixth nerve paresis, papilledema, and, in long-standing cases optic atrophy and even blindness. Ingestion of as little as 25,000 to 50,000 I.U. of vitamin A per day for as short a period as 30 days can induce signs of increased intracranial pressure. Nonspecific findings encountered at all ages include dry skin and mucous membranes, sparse hair, brittle nails, myalgia, bone pain, arthralgia, abdominal pain, splenomegaly and hypoplastic anemia with leukopenia.

Despite awareness of the potential dangers of vitamin A toxicity, the incidence of hypervitaminosis A appears to be increasing. Hypervitaminosis A may result through

* Proceedings of Workshop on Vitamin A. Food and Nutrition Board, January 28, 29, 1971. To be published.

easy availability of high potency vitamin preparations without prescription and by the overzealous parent who frequently administers vitamins under the popular premise, that, if one is good, two are better. The problem may be compounded by the use of bizarre, highly fortified health foods.

Serious problems of hypervitaminosis A have arisen in the use of large doses of vitamin A in treatment of acne vulgaris in adolescents. The clinical impression that high doses of vitamin A (50,000 I.U. to 150,000 I.U. per day) over a prolonged period are beneficial treatment for acne vulgaris has not been validated by well controlled clinical trials, nor is the rationale for this method of treatment clear.[19]

Vitamin supplements with proper levels of vitamin A for infants, children, adults, and pregnant women are available on the market. These should be prescribed when indicated. Vitamin supplements containing more than the daily doses recommended (6,000 I.U.) should not be used.

CONCLUSION

The grave risks resulting from the unrestricted sale of high concentrations of vitamin A make it imperative that an active curb, by appropriate legislation if necessary, be placed on the over-the-counter marketing of *high potency* vitamin A preparations. Physicians should be aware of the vitamin A content in the preparations they prescribe for their patients. They also should caution parents regarding the dangers of overdosage of this vitamin.

Committee on Drugs
SUMNER J. YAFFE, M.D., *Chairman*
Committee on Nutrition
L. J. FILER, JR., M.D., *Chairman*

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McMURRAY AND PENDERGAST
1019 19TH STREET, N.W.
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OND D. McMURRAY
IAM R. PENDERGAST
D J. ELIA

IRVING H. JUROW
New York Bar
CHARLES W. WHITMORE
Virginia Bar
OF COUNSEL

January 26, 1973

73

Miss Beryl S. McCullar
Hearing Clerk
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: Proposed Statement of Policy for Vitamins A and D, 21 CFR Part 3, December 14, 1972 [37 F.R. 26618]

Dear Miss McCullar:

We are counsel for Vitaminerals, Inc., Glendale, California, a company engaged in the manufacture and distribution of dietary supplements, including dietary supplements that contain Vitamins A and D. Vitaminerals intends to file comments on the agency's proposed statement of policy which would set maximum limitations on the use of these two vitamins in such dietary supplements. In order to be assured of preparing adequate, complete and scientifically correct comments, Vitaminerals requests that the time for filing such comments be extended to March 13, 1973.

Such an extension is needed by Vitaminerals because of the large number of published scientific articles dealing with the toxicity of these two vitamins. The FDA has already made available a partial list of these articles and Vitaminerals is now in the process of securing these articles, as well as the many others known to exist in the field. As of this date the company's scientific personnel are in the process of reviewing and evaluating over 100 such articles. This task is extremely complex since, in many cases, it is necessary to evaluate the

toxic reaction reported with the purpose for which the vitamin was used and the disease condition which may have been the occasion for the use of the vitamin. Additionally, since many of the articles cited and relied upon by the FDA report on toxic reactions in animals, it is necessary to convert the levels of vitamin ingested by the animals, in those articles, to a relevant level of anticipated use in humans. This is complex work, taking a great deal of time. Finally, some of the articles are in foreign languages and must be translated before they can be used at all.

All of this is, as you can appreciate, a major undertaking for a relatively small company such as Vitaminerals which is extremely interested in the proposed policy statement of the FDA, and, therefore, wishes to be heard on this subject.

Therefore, in order of being assured of the opportunity of making the best submission possible, Vitaminerals requests that the proposed extension of time for comments be granted. This will insure that all the pertinent data will have been fully and carefully reviewed and that therefore the most complete presentation possible of the views of an interested company, like Vitaminerals, will be made available to the agency. An early reply to this request will be appreciated.

Very truly yours,

William R. Pendergast

WRP/bmd

MEMORANDUM OF TELEPHONE CONVERSATION

BETWEEN: Dr. Malcolm A. Holliday
Chairman
American Academy of Pediatrics and Nutrition
and
Dr. Ogden C. Johnson

July 20, 1973

SUBJECT: Maximum Vitamin D Level in Food Products for Special Dietary Uses in Infant and Children

Dr. Johnson asked if Dr. Holliday had received comments from his committee on the proposal that a maximum of 1,000 International Units of Vitamin D be permitted in products designed to serve as primary or sole source of nutrition for infants with various diseases rather than the 400 provided for in the A and D document without prescription. Dr. Holliday said that no letters had been received; however, he had discussed it with several individuals. His opinion was that the committee's proposal should remain and that while the evidence was not complete in terms of keeping the limit at 1,000 there were a number of products that had proved useful in the marketplace and that it would be unfortunate to move these from over-the-counter to prescription. The products are used solely in the hospital and always under medical supervision. Their availability, however, should not be limited where in his opinion there is a need and very little if any risk. He said he would try to get back to FDA with comments as soon as he had received any letters.

Dr. Holliday also indicated that he wished to discuss the whole question of infant food labeling and infant formulas at the fall meeting of the Academy of Pediatrics. He tentatively was scheduling the meeting for October 31, two days prior to the regular meeting in which a small group of individuals would be asked to again discuss the whole problem of infant food labeling and how this can be accomplished. Dr. Johnson said that the regulations would be published within the next ten days and that while it was perfectly reasonable for the committee to discuss the whole question in light of the infant formulas that the Agency could not wait until October to publish the regulations. Dr. Holliday accepted this and said that he was still concerned that other ideas should be considered. Dr. Johnson said that he would make arrangements to have representatives of the Food and Drug Administration at the meeting, when the schedule had been set.

Ogden C. Johnson, Ph.D.
Acting Director
Office of Nutrition and
Consumer Sciences

cc: BF-262 (Mr. J. W. Boehne)

OCJohnke 8/9/73

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MARY CORNELIA BRADLEY MEMORIAL
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THE UNIVERSITY OF WISCONSIN

1300 UNIVERSITY AVENUE • MADISON, WISCONSIN 53706

July 9, 1973

Angel E. Salazar, M.D.
Medical Officer
Division of Metabolic and Endocrine Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

Dear Doctor Salazar:

Forgive my tardiness in answering your letter, but I have been out of town a great deal during the last three weeks.

As we discussed by telephone, I do not believe it advisable to allow the marketing of a non-prescription preparation containing more than 400 International Units of vitamin D daily at the recommended dosage. Conceivably, a food product, available without prescription would be useful for many patients with malabsorption or steatorrhea. For persons with those conditions, such a product might prove considerably less expensive if available without the necessity of obtaining a prescription. However, I believe that it would be unwise to include more than the recommended daily requirement of vitamin D in such a preparation. High potency vitamin preparations are available by prescription at relatively low cost. The maintenance of the prescription requirement for obtaining large doses of vitamin D might safeguard against either inadequate dosage in vitamin D-resistant conditions or vitamin D intoxication due to self-treatment by laymen.

I hope that this information will be helpful to you. Let me know if I can be of further assistance.

Sincerely yours,

Thomas H. Steele

Thomas H. Steele, M.D.
Renal Section
Department of Medicine

THS:dlt

STATION 3531

WASHINGTON UNIVERSITY
SCHOOL OF MEDICINE

CHROMALLOY AMERICAN KIDNEY CENTER
4949 BARNES HOSPITAL PLAZA
ST. LOUIS, MISSOURI 63110

July 11, 1973

Angel E. Salazar, M.D.
Medical Officer
Division of Metabolic and Endocrine
Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education, and Welfare
Rockville, Maryland 20852

Dear Dr. Salazar:

Concerning your letter of June 22, 1973, as you very well know, the physiological dose of Vitamin D ranges between 200-400 units per day. I am extremely concerned at the possibility of a product containing a 1000 units being available to the general public without a prescription. In the long range, an increased intake of Vitamin D could produce a significant degree of hypercalcemia and hypercalciuria.

By the same token, for people who have Vitamin D resistant rickets or osteomalacia, the amount of Vitamin D contained in this product, is extremely small and may not be effective at all. Thus, I strongly must oppose the marketing of this product without a prescription.

If there are any questions, please let me know.

Sincerely yours,

E. Slatopolsky

Eduardo Slatopolsky, M.D.
Associate Professor of Medicine

ES/fc

4650 SUNSET BOULEVARD NORMANDY 3-3341 MAILING ADDRESS P O BOX 54700 LOS ANGELES, CALIFORNIA 90054

Dr Angel E Salazar
Divisin of Metabolic and Endocrine Drug Products
Dept of HEW
Rockville, Md 20852.

July 15, 1973.

Dear Dr Salazar,

My apologies for this delay in responding to your letter of June 22, 1973 concerning the issue of "over the counter vitamin D without a prescription". I feel uncomfortable about this in view of the possibility of excessive intake by mistake or by intention with the concommitant hypercalcemia. In addition, I would also consider the incidences of malformed newborns in post-war England which may have some association with the addition of vitamin D to many food products, eg, bread.

I am willing to interact in any other way you and the Bureau would like and to supply any other information relating to this matter as newer data should arise.

With best wishes,

Yours sincerely,

James C M Chan, MD
Associate Professor

THE UNIVERSITY OF ARIZONA
ARIZONA MEDICAL CENTER
TUCSON, ARIZONA 85724

DEPARTMENT OF INTERNAL MEDICINE
ENDOCRINOLOGY SECTION

June 28, 1973

Angel E. Salazar, M.D.
Medical Officer
Division Metabolic andEndocrine Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Department of Health, Education, and Welfare
Rockland, Maryland 20852

Dear Dr. Salazar:

I am responding to your letter of June 22, 1973 regarding a) an over the counter product to be available without prescription containing 1000 IU of Vitamin D b) a complete food product to be used by persons having poor Vitamin D absorption, steatorrhea, or fat malabsorption available without prescription but labelled to be used under medical supervision. I see no need for either of these products and in view of the serious toxicity of D over-administration I think it would be dangerous to allow these drugs to be distributed over the counter.

Sincerely,

C. A. Nugent

C. A. NUGENT, M.D.
Professor and Head
Section of Endocrinology

CAN:vg

VETERANS ADMINISTRATION
WADSWORTH HOSPITAL CENTER
WILSHIRE AND SAWTELLE BOULEVARDS
LOS ANGELES, CALIFORNIA 90073

493a

August 1, 1973

IN REPLY
REFER TO: 691/111L

Angel E. Salazar, M.D.
Medical Officer
Div. of Metabolic and Endocrine Drug Products
Office of Scientific Evaluation
Bureau of Drugs
Food and Drug Administration
Rockville, Maryland 20852

Dear Dr. Salazar:

Regarding your letter of June 22, 1973, inquiring about the need for an Over-the-Counter product containing 1000 IU of Vitamin D, it is my opinion that such a product would pose far too many hazards to make it worthwhile. Thus, there may be a need for a "complete food product", in those having poor vitamin D absorption or steatorrhea, but I feel that such patients should be under close surveillance by a physician and should have the quantity of vitamin D tailor made. The use of such a product without prescription might indeed lead to its being taken by those not needing vitamin D with the possibility that long-term ingestion might lead to toxicity.

Therefore, I would oppose having such a product available. I hope that this answers your request.

Sincerely yours,

JACK W. COBURN, M.D.
Chief, Nephrology Section and
Professor of Medicine
UCLA

Show veteran's full name, VA file number, and social security number on all correspondence.

THE HOSPITAL OF ST. RAPHAEL
1450 CHAPEL STREET
NEW HAVEN, CONNECTICUT 06511
TELEPHONE 772-3900

494a

NORMAN J. MARIEB, M.D.
DEPARTMENT OF INTERNAL MEDICINE

June 29, 1973

Angel E. Salazar, M.D.
Medical Officer
Div. of Metabolic and Endocrine Drug Products
Public Health Service
Food and Drug Administration
Rockville, Maryland 20852

Dear Doctor Salazar:

In reply to your letter of June 22, 1973, I believe it would be appropriate to have an over-the-counter medication with 1000 units of Vitamin D for those patients with malabsorption and those taking anticonvulsive agents. Also, a complete food product as long as it is used under medical supervision, could be placed on the market without necessarily having to be a prescription drug. I do not see any contraindication in having this type of diet available.

I hope this response satisfies your request.

Sincerely yours,

Norman J. Marieb, M.D.

NJM:emc

March 7, 1974

Abel L. Robertson, Jr., M.D., Ph.D.
Professor
Case Western Reserve University
Institute of Pathology
Cleveland, Ohio 44106

Dear Dr. Robertson:

Your letter addressed to Dr. Alexander Schmidt, Commissioner of Food and Drugs, was referred to me for reply to the specific comment on the new FDA regulations on vitamins and minerals.

In response to the notice published in the Federal Register, December 14, 1972, proposing that preparations containing vitamin D in excess of 400 I.U. per dosage unit will be dispensed on prescription, approximately 2500 comments were received. Comments from organized medicine were presented by the American Medical Association and the American Academy of Pediatrics. They agreed that the action proposed by FDA was necessary and that the prescription levels for vitamin D is suitable.

All vitamins including vitamin D are currently being reviewed by an Over-the-counter (OTC) Drug Advisory Review Panel. Safety and effectiveness and more general questions related to adequate labelling of vitamin preparations marketed as OTC drugs are being considered by the panel. In addition, they are also considering differences between foods for special dietary use, OTC drugs and prescription drugs as they relate to vitamins.

Until such time as the OTC Drug Advisory Review Panel has completed its review and the new regulations are in effect, the FDA is permitting the use of vitamin D at levels not to exceed 400 IU per dosage unit and the recommended daily dosage should not exceed 400 I.U. in preparations offered either as a dietary supplement or OTC drugs. These figures are within the Recommended Dietary Allowances established by the Food and Nutrition Board - National Research Council, and the National Academy of Sciences.

The FDA will publish, in the near future, new regulations governing dietary supplements of vitamins and minerals.

DESI Vit A + D.

file cy

In view of your interest and concern, we invite you to forward references to scientific articles published or unpublished dealing with vitamin D and development of diffuse atherosclerosis, for consideration by the Review Panel.

We were pleased to note that you found the information in the FDA Drug Bulletin on vitamins and minerals helpful. This is one of the ways by which we plan to communicate regularly with the professional members of the community.

We look forward to receiving your comments on this or any other related matter with interest.

Sincerely yours,

[redacted]

Joginder C. Chopra, M.D.
Medical Officer
Division of Nutrition

cc:
HFF-262 (Mr. J.W. Boehne)
HFF-1 (Lucille Craft)
HFE-224

HCCHOPRA:dlh 3/7/74

497a

March 19, 1974

Joginder G. Chopra, M.D.
Medical Officer
Division of Nutrition
Dept. of Health, Education and Welfare
Food and Drug Administration
Washington, D.C. 20204

Dear Dr. Chopra:

Thank you for your reply of March 7.

Regarding your request for information on the synergistic effects of excess dietary vitamin D on induction of experimental and clinical vascular disease, the following comments may be pertinent.

In small laboratory animals, such as the adult Sprague Dawley rat, a total dose of 1400 I.U. of vitamin D may produce severe vascular changes with medial metastatic calcification of major arteries resembling Mönckeberg's lesions in man. Such lesions may appear without clinical hyperparathyroidism and are histologically and ultrastructurally similar to vascular changes we are now finding in our laboratory in patients undergoing chronic renal dialysis and clinical manifestations of sustained hypercalcemia.

Definitive clinical data regarding the long-term vascular effects of the recommended daily allowance of vitamin D (400 I.U.) in infants and young children is not yet available and should be carefully studied. It seems reasonable, however, that chronic administration to youngsters of adult doses of vitamin D in breakfast cereals, when combined with large ingestion of vitamin D supplemented milk and other dairy products, although insufficient to produce acute toxic symptoms, could induce accelerated development of vascular disease. The increased incidence of endemic athero-arteriosclerosis in well fed Americans seems to substantiate the need to reconsider the medical rationale for vitamin D supplementation.

I look forward to hearing from you regarding future FDA efforts and suggestions on this matter of great concern in our pediatric practice.

Very truly yours,

Abel L. Robertson, Jr., M.D., Ph.D.
Professor of Pathology

...itute of Pathology

THE UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 TWINBROOK PARKWAY, ROCKVILLE, MARYLAND 20852
(301) 881-0666

...F TRUSTEES
...NT
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...Tice, D.Sc.
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...Eisenbrandt, Ph.D.
...Mahaffey, D.Sc.
...VE DIRECTOR
...RETARY
...Holler, Ph.D.

April 25, 1974

Mr. Robert E. Pinko
HFD-109
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Pinko:

I trust that since our conversation after the National Drug Advisory Committee meeting that all has been going well in your new position. I've got a minor problem which I hope you can help me with. Let me get to the point.

In Regulation 21CFR part 125.5(c)(5), appearing in the August 2, 1973 issue of the Federal Register, the Commissioner concluded that International Units shall be utilized as the standard units of measurement for Vitamins A and D. It is my understanding that this regulation applies to foods for special dietary uses.

Regulations 3.94 (Vitamin A preparations for oral use as drugs) and 3.95 (Vitamin D preparations for oral use as drugs) appear in the same issue and describe conditions for the sale of these preparations and contain labeling requirements based on the amounts of Vitamin A or D contained therein. While regulations 3.94 and 3.95 utilize International Units in explaining the dosage limitations of these drug items, they do not indicate whether USP Units or International Units are to be actually utilized in the labeling.

Currently the United States Pharmacopeia requires Vitamin A and Vitamin D to be labeled in terms of USP Units. While the change in regulation 125.5(c)(5) from USP Units to International Units for foods is stated to have been a technical change, such may not be the case for drugs. Let me explain why.

(1) Presently, the USP Reference Standards for ergocalciferol (Vitamin D) and Vitamin A (retinol) constitute the basis of measurement or comparison for these vitamins in the United States. The methods of analysis for these drugs are based upon USP Units and the utilization of USP Reference Standards. I do not believe International Reference Standards necessary to determine the amount of International Units present are as readily available in this country, and their unavailability might cause some difficulties.

(2) Although USP Units are currently equivalent to International Units, USP Units may in the future differ if American scientists justifiably disagree with the way an international reference standard is established or is replaced. This has happened in the past with other drugs when one lot of International Reference Standards was replaced by a lot giving different results, thus failing to provide continuity in the potency of drug products on the market. I don't know the likelihood of this, but it seems that it is something which should be considered before a change for change's sake is made.

(3) We are hesitant to change USP monograph labeling requirements for these drugs until the recommendations of the FDA Advisory Committee for Vitamins and Minerals are known.

If you agree with my interpretation of these regulations, a couple of possible solutions come to mind. (1) USP Units could continue to be utilized in the labeling of drug products. This might have an advantage in that it might serve to emphasize the "drug" nature of these articles to the professions and the public and would distinguish them from foods. (2) A statement could be published indicating that it is acceptable to use Reference Standards in analytical procedures to measure the potency of Vitamins A and D even though the labeling may, for the consumer's benefit, indicate the quantity present in International Units. (3) Alternatively, 21CFR 125.5(c)(5) could be amended indicating that USP Units are also acceptable for labeling purposes. (4) We could, if the FDA Advisory Committee so recommends, modify the Pharmacopeial requirements to require labeling of drug products to be in International Units.

May I have your comments. Thank you for your consideration.

Best wishes,

Joseph G Valentino

JGV:jak

Joseph G. Valentino, J.D.
Executive Associate

RECEIVED
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OTC Staff/NSE
Bureau of Drugs
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

June 14, 1974

Joseph G. Valentino, J.D.
Executive Associate
The U.S. Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, Maryland 20852

Dear Mr. Valentino:

This replies to your letter of April 25 to Mr. Robert Pinko. We agreed to comment on the vitamins A and D nomenclature issue you raised.

I believe you can understand that the FDA proposal in August, 1973 (38 FR 20749) and the follow-up decision in February, 1974 (39 FR 5313) were done in the interest of conformity where differences might have been confusing to both the lay public and the professionals in health sciences. As you implied, our sights were primarily on foods, not drugs.

The USP Reference Standards for both vitamin A and vitamin D (and others) have been invaluable over the years for vitamin analytical laboratories, including of course our own. If there are no other equivalent reference standards developed and available for these purposes, we would like to see the USP standards continued. As you know, the trend has always been to relate vitamin potency to the weight of a specific chemical compound when that is possible. I believe that at one time, although there was never a USP Unit for vitamin C, 1 IU was equal to 50 mcg of the USP Ascorbic Acid Reference Standard. Whether nutritionists and clinicians will ever refer to vitamin E potency in terms other than International Units (IU) is hard to say. I frankly do not see any value served in perpetuating a situation in which one nomenclature is used when a substance is a drug and another when it is a food. Technically, under the FD&C Act, there are situations when a substance can be both a food and a drug. It would seem reasonable to express potency of reference standards in terms of weight, whenever possible.

In the case of the USP Vitamin D Reference Standard, this might take the form of "0.025 mcg cholecalciferol (1 USP Unit) per ____cc."

Any differences between the definitions of the USP Unit and IU for either vitamin D or vitamin A are not likely to arise in the near future, I would hope. The fact that the United States has been and will continue to be represented in the International Union of Nutritional Sciences (IUNS) (in which there is a specific Committee on Nomenclature) should make for better cooperation in the international community.

Every indication, so far, is that the Advisory Review Panel on OTC Vitamin, Mineral and Hematinic Drug Products will recommend nomenclature adopted by the IUNS. They are using IU in lieu of USP Units in their current deliberations. For a period of time, perhaps five years, it seems reasonable to me that both "USP Unit" and "IU" terms might be used. This is analagous, in a sense, to what is being done in labeling during the changeover from the English to the metric system of weight. In other words, the optional parenthetical designations of USP Unit could be used (i.e., vitamin D, 400 IU (USP Units) per quart - or per tablet).

There are similar situations which deserve discussion and resolution between USP and FDA on nomenclature. One is the simple matter of the spelling of thiamin without an "e." "Thiamine" is obsolete; however, FDA felt compelled because of the USP monograph to retain the "e" in the August 2, 1973, Federal Register publications.

If we can be of any further help in trying to resolve these and other issues of nomenclature of substances that fall into the categories of foods and drugs, please don't hesitate to write.

Sincerely yours,

J. William Boehne
Assistant Director
Division of Nutrition

FEB 1 2 RECD

FEB 3 1975

Honorable Paul G. Rogers
House of Representatives
Washington, D.C. 20515

Dear Mr. Rogers:

This is in reply to a December 11, 1974 telephoned request from Mr. Dack Dalrymple of your staff concerning information on deaths and injuries from overdoses of vitamins A and D.

We do not have a complete tabulation of the number of deaths or injuries due to overdoses of vitamins A and D which have been reported in the literature. Such a tabulation probably would not be accurate or meaningful, since the scientific community believes that overdosage reactions to vitamins A and D are under-reported. Mr. Dalrymple indicated, however, that if such data were not available, he would need a list of the various adverse reactions to these vitamins. They are given below (with available statistics).

Vitamin A

The only death we are aware of that has been attributed to excessive doses of vitamin A was recorded in England (see enclosed article from The New York Times, February 17, 1974). We have requested additional information regarding this death.

We are aware of vitamin A overdosage reports of 66 persons (39 adults) who received medical attention for intracranial manifestations such as increased pressure. Increased intracranial pressure can mimic brain tumors and has resulted in instances of needless neurosurgical intervention. Symptoms of excessive vitamin A intake include: anorexia; hyperirritability; skin lesions; bone decalcification; headache; nausea; vomiting; weight loss; hair loss; bone, joint, and muscle pain; skin disorders (rash, peeling of large areas of skin, itching); and enlargement of the spleen and liver, including liver cirrhosis.

Vitamin D

Deaths attributed to vitamin D overdosage reported in the world literature include: 3 in the United States, 5 in Great Britain, 2 in Finland, 1 in Germany, 1 in Canada, and 1 in Australia.

Reports of injuries are as follows:

(a) idiopathic hypercalcemia of infancy: Great Britain 225, France 2, Russia (a 1959 report) 3, Finland 11;

(b) hypercalcemia: United States 45, Great Britain 5 (adults)

(c) permanent renal damage: Italy (2 reports) 12, Spain 1, United States 1;

(d) congenital malformations: Great Britain 11, Italy 2, Germany 10, United States 13.

Symptoms of vitamin D overdosage are weakness, fatigue, lassitude, headache, nausea, vomiting, diarrhea, and renal impairment.

As requested by Mr. Dalrymple, we enclose several articles from scientific journals which cover specific cases of injury due to vitamin A and D overdosage. We hope they will serve your needs.

Please let us know if we can be of further assistance.

Sincerely yours,

Robert C. Wetherell, Jr., Director
Office of Legislative Services

17 Enclosures
Cy News Clipping 2/17/74
Repr "Vitamins" - CBM Dalderup
Repr A.M.A. American J. - Diseases of Children - Acute Hypervitaminosis A - Marie et al
Repr 12/21/68 Birtish Med. J. - Vitamin D. Intoxication . . .
Repr A.M.A. American J. - Diseases of Children - Hypervitaminosis A - Knudson et al
Repr 8/18/73 Med. J. of Australia - Chronic Vitamin A Intoxication
Repr 4/8/39 J.A.M.A. - Vitamins A Deficiency . . .
Repr 8/28/67 J.A.M.A. - Chronic Hypervitaminosis A - Benedetto
Repr 6/73 J. Clinical Nutrition - Acute Hypervitaminosis - Furman
Repr 2/70 American J. Dis Child/Vol. 119 - Hepatic Injury . . . Rubin et al
Repr 1/74 Annals Intern, Med. - Hypervitaminosis A - Frame et al

Page 3 - Honorable Paul G. Rogers

Repr Annals Intern. Med. 7/74 - Hypervitaminosis . . .
  Lebow et al
Repr 9/14/74 British Med. J. - Vitamin D . . .
  Linden
Repr J.A.M.A. 8/24/70 Papilledema . . .
  Morrice
Cy ltr to FDA Div. Epidemiology and Drug Experience
Repr J.A.M.A. 4/27/70 - Case Report - Fedotin
Repr J.A.M.A. 5/54 - Vitamin A Poisoning . . .
  Gerber et al

cc: Congressional Liaison Office

cc: HFL-10 (2)
  HFF-262
  HFF-200
  HFF-314
  HFD-130 (Ortiz)

R/D:HFD-30:MJFromer:dsi:1/20/75
R/D:Init:MJFromer:1/21/75
  WBraunig:HFL-10
F/T:jab:1/29/75

505a

March 29, 1974

Abel L. Robertson, Jr., M.D., Ph.D.
Professor
Case Western Reserve University
Institute of Pathology
Cleveland, Ohio 44106

Dear Dr. Robertson:

Thank you for your letter of March 19th attached providing information on the effects of high doses of vitamin D on Sprague Dawley rat.

We have taken the liberty of transmitting your views to the Committee on Nutrition - American Academy of Pediatrics and the Over-the-Counter (OTC) Drug Advisory Review Panel for consideration during deliberations on this subject.

Your providing us with specific references of published material demonstrating the relationship between vitamin D and metastatic calcification of major arteries would be useful for reviewing the matter fully.

We look forward to receiving any additional information you may have in this regard.

Sincerely yours,

SIGNED

Joginder G. Chopra, M.D.
Medical Officer
Division of Nutrition

cc:
HFF-262 (Mr. J.W. Boehne)

JGCHOPRA:dlh 3/29/74

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file

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AF 3-027
Arcon Manufacturing Company
Los Angeles, California

August 3, 1973

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Annette Dickinson, Arcon Manufacturing Company, Los Angeles, California

and Sam D. Fine, Associate Commissioner for Compliance

Subject: Status of Vitamin A and Vitamin D (SPI 3.94--FR of 8/2/73)

Ms. Dickinson telephoned Associate Commissioner for Compliance Sam D. Fine on August 2, 1973, to discuss the effective date of the Order referred to above. She said it was her interpretation that products received in bulk by Arcon could continue to be labeled in the same manner until 60 days after August 2, 1973. Mr. Fine obtained his copy of the Federal Register document, and after his review, informed Ms. Dickinson that he agreed with her interpretation. He pointed out that FDA intends to allow an orderly reformulation and relabeling, and that no recall of existing stocks is deemed necessary. Ms. Dickinson thanked Mr. Fine for his interpretation.

Sam D. Fine

Sam D. Fine

cc: OC-1 OC-2 CC-1 CC-2
BF-1 BF-310 GC-1
BD-1 BD-300 BD-310

SDFine:eh 8/3/73

SPECIAL REPORT

507a

BEST COPY AVAILABLE

HAZARDS OF OVERUSE OF VITAMIN D

A Statement of the FOOD AND NUTRITION BOARD, NATIONAL ACADEMY OF SCIENCES, NATIONAL RESEARCH COUNCIL

Prepared by the Committee on Nutritional Misinformation

An excess intake of vitamin D can result in serious toxicity. Vitamin D is stored in the fatty tissues of the body and is present in the circulating plasma. Because vitamin D promotes absorption of calcium from the intestine, a large excess of stored vitamin D can cause excessive quantities of calcium in the blood (hypercalcemia) persisting for months after intake of vitamin D has been discontinued. Chronic hypercalcemia causes calcification of soft tissues with particularly serious injury to the kidney; associated general symptoms are weakness, lethargy, anorexia, and constipation. The sensitivity of individuals to an excess of vitamin D is quite variable so that it is not possible to state the minimal toxic dose. Overuse of vitamin D in England and the European continent during the 1940's and 1950's is thought to be the cause of a serious disorder of infancy called "idiopathic hypercalcemia" that was seen with unusual frequency in that period. Following reduction of vitamin D intake to levels approximating those considered adequate in this country, "idiopathic hypercalcemia" has become quite rare.

Vitamin D is an unusual nutrient in that its major natural source is not food, but rather the 7-dehydrocholesterol in the skin, which is converted to vitamin D by the short wave ultraviolet component of sunshine. The usual foods of infants including breast milk contain little vitamin D. Without exposure to sunshine or fortification of the diet with vitamin D, vitamin D deficiency results in infants. In some industrial cities of the temperate zones infants may not get sufficient exposure to ultraviolet light because of the combination of climatic conditions and atmospheric smog. Smog absorbs most of the sun's short wave ultraviolet light radiation even on sunny days. For this reason rickets, a disease resulting from defective mineralization of bone due to lack of vitamin D, was once extremely common in infants and children in northern Europe and the United States. Because of the widespread use of vitamin D-fortified milk and infant feeding preparations, rickets has become an exceedingly rare disease in this country.

The vitamin D requirement of infants during the rapidly growing period of the first six months of life, can, and has been, accurately determined. In this age period a daily intake of 400 I.U. of vitamin D is adequate with an ample margin of safety for normal biological variation. For most infants 100 I.U. per day in milk would probably suffice. Vitamin D is also required by older children and adults but determination of the true requirement beyond infancy is extremely difficult, and the assumption has been made that a daily intake of 400 units meets the needs beyond infancy as well. This seems justified by our present experience. In the adult, the poor mineralization of bone resulting from vitamin D deficiency is termed osteomalacia.

August 3, 1973

Kellogg Company
Battle Creek, Michigan 49016

Attn: William C. Morris, Ph.D., Nutritionist

Dear Dr. Morris:

Your answer of July 30, regarding vitamin D supplement in your K 19 cereal is far from clear. The nature of the "gross physiological toxicity symptoms" mentioned in your letter deserves careful definition. It is indeed hard to understand what a "physiological" toxic is since in current medical usage physiology, in contrast to pathology, relates exclusively to the study of normal functions.

Secondly, contrary to review references provided in your letter of July 30, there have been a number of studies including experimental work on dystrophic and metastatic calcification (see Dr. H. Selye's extensive bibliography) showing that oral administration of 1,000 I.U. of vitamin D in a 200 g normal rat suffices to produce dermatomyositis and cutaneous calcinosis. More importantly, in regard to man, arterial calcifications with chronic lesions resembling typical arteriosclerosis are also created.

It seems reasonable, therefore, that chronic administration of adult doses of vitamin D in breakfast cereals, when combined with large ingestion of vitamin D supplemented milk and other dairy products, although insufficient to produce acute toxic symptoms, could induce accelerated development of vascular dystrophic calcification and diffuse arteriosclerosis.

The increased incidence of this endemic disease in well fed Americans seems to substantiate the need to reconsider the medical reasons for vitamin supplements in our children's diet.

Sincerely yours,

Abel L. Robertson, Jr., M.D. Ph.D.
Professor of Pathology

ALR:jc

cc: FDA, Washington, D.C.

509a

Vit. A + D Reg.

NEWS RELEASE

FOOD AND DRUG

72-92

Edward R. Nida: 301 443-3285
Home Phone: 301 365-4574

VITAMINS A and D PRODUCTS

FOR RELEASE: PLEASE OBSERVE EMBARGO
P.M.'s - Wednesday December 13, 1972

The Food and Drug Administration today acted to limit the strength of Vitamin A and D products available for self-treatment without a prescription.

FDA's objective is to establish safe amounts of vitamins that can be effective as dietary supplements for use by consumers. Based on current scientific knowledge the Agency is proposing daily limits of 10,000 International Units (I.U.) for vitamin A and 400 I.U. for vitamin D. These figures are within the recommended daily dosages established by the Food and Nutrition Board, National Academy of Sciences - National Research Council. In the United States this board is the recognized authority for determining vitamins and their nutritional requirements on humans.

The principal effect of the proposed regulations will be to have makers of multivitamins revise their formulas. Many multivitamin products are presently below the limits proposed for vitamins A and D. There are on the market, however, vitamin A products in dosages 10 times the recommended daily allowance (RDA) and vitamin D products 60 times the RDA.

-MORE-

High-doseage vitamin products prescribed by physicians for specific patients will be unaffected.

Both vitamins are recognized as necessary to good human nutrition. However, excess amounts can be dangerous to both adults and children.

Reports of misuse of large doses of both vitamins A and D have prompted medical groups and FDA to seek limitations on them. Widespread promotion of both vitamins has resulted in excessive use for conditions such as acne, night blindness, and arthritis. Neither vitamin A nor D are proven effective for these conditions in well nourished people.

Excessive amounts of vitamin A taken over long periods can increase pressure within the human skull and may mimic a brain tumor. Large doses of this vitamin have also been shown to retard growth in children. Vitamin D has been known to retard mental and physical growth in children.

In commenting on the proposal, Dr. Charles C. Edwards, Commissioner of Food and Drugs, said: "Vitamins A and D are known to be toxic; and they are heavily promoted in high doses to the consumer; and we continue to accumulate evidence of adverse effects from excessive intake." "The FDA has concluded, therefore, that consumer safety requires the action we are taking."

Interested persons may submit written comments within 60 days. Comments should be addressed to the Hearing clerk, Department of Health Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Maryland 20852.

# # # #

CC: Dr. Chase
Dr. Foód.
Dr. Campbell

511a

HAZARDS OF OVERUSE OF VITAMIN D

A Statement of the

FOOD AND NUTRITION BOARD

DIVISION OF BIOLOGICAL SCIENCES

ASSEMBLY OF LIFE SCIENCES

NATIONAL RESEARCH COUNCIL

(Prepared by the Committee on Nutritional Misinformation)

NATIONAL ACADEMY OF SCIENCES

November, 1974

NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, acting in behalf of the National Academy of Sciences. Such approval reflects the Board's judgment that the project is of national importance and appropriate with respect to both the purposes and resources of the National Research Council.

The members of the committee selected to undertake this project and prepare this report were chosen for scholarly competence and with due consideration for the balance of disciplines appropriate to the project. Responsibility for the detailed aspects of this report rests with that committee.

Each report issuing from a study committee of the National Research Council is reviewed by an independent group of qualified individuals according to procedures established and monitored by the Report Review Committee of the National Academy of Sciences. Distribution of the report is approved, by the President of the Academy, upon satisfactory completion of the review process.

HAZARDS OF OVERUSE OF VITAMIN D

An excess intake of vitamin D can result in serious toxicity. Vitamin D is stored in the fatty tissues of the body and is present in the circulating plasma. Because vitamin D promotes absorption of calcium from the intestine, a large excess of stored vitamin D can cause excessive quantities of calcium in the blood (hypercalcemia) persisting for months after intake of vitamin D has been discontinued. Chronic hypercalcemia causes calcification of soft tissues with particularly serious injury to the kidney; associated general symptoms are weakness, lethargy, anorexia, and constipation. The sensitivity of individuals to an excess of vitamin D is quite variable so that it is not possible to state the minimal toxic dose. Overuse of vitamin D in England and the European continent during the 1940's and 1950's is thought to be the cause of a serious disorder of infancy called "idiopathic hypercalcemia" that was seen with unusual frequency in that period. Following reduction of vitamin D intake to levels approximating those considered adequate in this country, "idiopathic ~~hycalcemia~~ hypercalcemia" has become quite rare.

Vitamin D is an unusual nutrient in that its major natural source is not food, but rather the 7-dehydrocholesterol in the skin, which is converted to vitamin D by the short wave ultraviolet component of sunshine. The usual foods of infants including breast milk contain little vitamin D. Without exposure to sunshine or fortification of the diet with vitamin D, vitamin D deficiency results in infants. In some industrial cities of the temperate zones infants may not get sufficient exposure to ultraviolet light because of the combination of climatic conditions and atmospheric smog. Smog absorbs most of the sun's short wave

ultraviolet light radiation even on sunny days. For this reason rickets, the disease resulting from defective mineralization of bone due to lack of vitamin D, was once extremely common in infants and children in northern Europe and the United States. Because of the widespread use of vitamin D-fortified milk and infant feeding preparations, rickets has become an exceedingly rare disease in this country.

The vitamin D requirement of infants during the rapidly growing period of the first six months of life, can, and has been, accurately determined. In this age period a daily intake of 400 I.U. of vitamin D is adequate with an ample margin of safety for normal biological variation. For most infants 100 I.U. per day in milk would probably suffice. Vitamin D is also required by older children and adults but determination of the true requirement beyond infancy is extremely difficult, and the assumption has been made that a daily intake of 400 units meets the needs beyond infancy as well. This seems justified by our present experience. In the adult, the poor mineralization of bone resulting from vitamin D deficiency is termed osteomalacia. Nutritional osteomalacia due to lack of vitamin D has been described particularly in elderly patients on highly restricted diets estimated to provide less than 100 I.U. of vitamin D per day. The normal child, the adult, and the pregnant or lactating woman do not require more than 400 I.U. of vitamin D per day. These normal requirements are met by exposure to sunshine and consumption of such foods as vitamin D-fortified milk, egg yolk, and fish, such as salmon, sardines, herring, and tuna. The use of vitamin D concentrates is necessary for breast fed infants and infants on non-fortified milk but is rarely required for the proper vitamin D nutrition of other infants, children, or adults.

Use of highly concentrated preparations of vitamin D may be required by patients with specific diseases requiring unusual amounts of vitamin D. This treatment must be closely supervised by a physician. Vitamin D must be metabolized in the liver and kidney before it becomes the active compound that regulates the calcium and phosphate metabolism of the body and ensures normal bone mineralization. The vitamin D requirements of patients with liver disease and kidney disease must be separately determined and such patients may require much greater amounts of this vitamin than is normally given. Because of poor absorption of vitamin D by patients with intestinal malabsorption increased amounts of dietary vitamin D are needed in their treatment.

In summary, excessive amounts of vitamin D are hazardous and only individuals with diseases affecting vitamin D absorption or metabolism require more than 400 I.U. per day. Such needs should be established by clinical evaluation, and treatment should be specifically recommended and supervised by physicians.

REFERENCES

American Academy of Pediatrics Committee on Nutrition. The relation between infantile hypercalcemia and vitamin D-public health implications in North America. Pediatrics 40:1050, 1967.

Gough, K. R., Lloyd, O. C., and Willis, M. R. Nutritional Osteomalacia, Lancet ii: 1261, 1964.

Harrison, H. E. Calcium Metabolism in Pediatrics, 15th Edition, H. L. Barnett, ed., Appleton-Century-Crofts, 1972, New York.

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

- - - - - - - - - - - - - - - - - - - x

NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs

vs. 73 Civil 3448 (MSF)

DAVID F. MATHEWS,

Defendant

- - - - - - - - - - - - - - - - - - - x

Before:

Hon. Marvin E. Frankel,

District Judge

New York, N. Y.

May 28, 1976 - 4.35 P.M.

APPEARANCES:

Bass, Ullman & Lustigman, Esqs.,
Attorneys for Plaintiffs
By: Milton Bass, Esq., of Counsel

Robert B. Fiske, Jr., Esq.,
United States Attorney
For the Defendant
By: Naomi Reice Buchwald, Esq.,
Assistant United States Attorney

THE COURT: First, I am not sure why this goes along at such a leisurely pace. The papers get filed in a rather luxurious schedule. I take it your clients are not in a terrible hurry, Mr. Bass?

MR. BASS: They are in a hurry, your Honor.

THE COURT: Their lawyers are not in a very great hurry.

MR. BASS: We have been trying to be reasonably so, your Honor.

THE COURT: If you are in a hurry, we will move along quickly. The rate at which the papers have been filed suggests otherwise. But I will try to get this out quickly, and I will press both of you and me to do that.

First, we have gotten out of our files - that is, Mr. Jackson has gotten out of our files - the numerous folders of things that I understand comprise the record at this moment. What I want to know is this: Are the files that are lodged in the district court now the same "record" as the one that was before the Court of Appeals?

MR. BASS: Yes, sir.

MS. BUCHWALD: Yes, sir.

THE COURT: You both agree on that.

The opinion of the Court, Judge Mansfield's

opinion, intimates that there may have been something less than the full record before the Court of Appeals. I want to know what that intimation meant to both of you and what we should plan to do about that.

MS. BUCHWALD: Your Honor, I don't know exactly what Judge Mansfield meant. But, pursuant to your Honor's instruction, we did cause an extensive search of the FDA's files to be made. I have --

THE COURT: I don't think you understood my question. My first question is, was there anything less before the Court of Appeals than that which had been before me?

MS. BUCHWALD: No, sir.

THE COURT: Now go on with what you were saying.

MS. BUCHWALD: As I was beginning to say, we conducted an extensive search of the FDA's files, and I have with me in court all material that we were able to locate remotely related to these vitamin A and D regulations.

Most of that material we believe is not properly made part of the record, for reasons I will describe in a minute. However, in preparing for this argument today I reread through all the material I had in my office and I believe that there are a number of letters which might,

arguably, be considered part of the record and I would be prepared to submit those to Mr. Bass and to your Honor now.

These are letters from physicians or, in one case, a memorandum of a telephone conversation with a physician and a doctor at FDA, which communications occurred during the period beginning with the proposal of the regulation and concluding with the regulation's actual promulgation.

These are the only materials which I believe could arguably be made part of the record.

THE COURT: The folders that are before me now, which I look forward to reading from cover to cover in the next week or so, are they marked in some way seriatim? How are they identified?

MS. BUCHWALD: They really are not, your Honor. Those are the comments submitted in response to the regulation. Part of that proposal says that anyone who has a comment should --

THE COURT: I know what they are. But they are not marked in any way?

MS. BUCHWALD: No, sir.

THE COURT: They are alleged to be all the comments the FDA received?

MS. BUCHWALD: Which were filed with the

Hearing Clerk.

THE COURT: The things you have in your hand, which you say you are willing to add to the record, I direct should be added to the record, and let's put them in a folder called "Supplemental Record." You put that in that kind of manila folder and then we will all know what we are talking about when you go back up to higher courts.

Be sure you have that in such a folder, because I will look at it in that light.

What are these other things you say you have but which you don't believe ought to be made part of the record?

MS. BUCHWALD: Your Honor, the other material can be described briefly as follows:

There are intra-agency memoranda with respect to the proposed regulation. There is correspondence with persons outside the agencies which either pre-dates or post-dates a period which I spoke of earlier, namely from the date the regulation was proposed to the date it was enacted.

There is also some medical articles and there are also drafts --

THE COURT: Medical articles which were in the files of the agencies?

MS. BUCHWALD: Which were. But I cannot assure your Honor whether they were in the files. Some of the medical articles I recognize as being part of the record which is presently before your Honor, some of the medical articles I do not recognize, and I am fairly familiar with the medical articles which were before your Honor.

THE COURT: Without reading all the Law Review literature as to what constitutes the administrative record in a rule-making proceeding, and without reexamining what the Administrative Conference and Walter Gelhorn and God have said about this, if that pile of papers which you say is not part of the record --

How many papers are we talking about? You are holding up an envelope about an inch and a half thick?

MS. BUCHWALD: Right.

THE COURT: If that sheaf of papers were handed to Mr. Bass to read in conjunction with hisattack on your vitamin A and D regulations, would it affect any considerations of privacy or security that are important?

The reason I ask that is this: If I have to make a decision in advance of deciding this case as to what constitutes a record, for good and sufficient reason I will do it. On the other hand, if I don't and I allow some things to be disclosed to Mr. Bass that, strictly speaking,

are not part of the record, and he exploits them, then it seems to me the Court of Appeals will have the whole business in one fell swoop, and if these things were given to him erroneously, whatever mistaken result that has they can fix. If they were withheld from him erroneously, they can't fix it; they have to send it back here. And, as much as I love seeing you both, one more remand of this would be one more remand than I really need.

If you gave him that stuff without prejudice, just understanding that it was in the support of a trial judge's effort to expedite the work, would the FDA be hurt?

MS. BUCHWALD: I think that with respect to some of the material, it would.

THE COURT: Why?

MS. BUCHWALD: Because I think there are two principles which we have tried to protect here, which I think are important ones. One is the privilege given to the Government for its intra-agencies deliberative communications, its thought process. That, we believe, should be protected, and it has been continually protected in the Freedom of Information Act and by the courts before that.

The second one is that we are really being consistent with the other principle that your Honor has applied to this case, and that is the Morgan principle, that

we do not invade the mind of the decision maker in the absence of showing bad faith.

THE COURT: Let's narrow this conversation. I am morally prepared to sustain your view with respect to intra-agencies' exchanges of views and I imagine I will so hold, even if it means another appeal, because I think that is correct. But you mentioned other things that are in that folder.

If I sustain you on the intra-agencies thing, what about the rest of the stuff in the folder?

MS. BUCHWALD: There is certainly no problem, or no significant principle, that we would be protecting by withholding medical articles.

THE COURT: Right.

MS. BUCHWALD: As to comments that are outside the period, I think that I would just like the opportunity to consult with the FDA on that, and I think there is room for flexibility. Clearly, everything that is after the regulations we are not relying on and it is irrelevant to the lawsuit.

THE COURT: Now, do me a favor. Make a folder of intra-agencies' communications which you will hand up to me Tuesday, or something, and unless Mr. Bass quickly talks me out of it I am going to let you keep those.

But I am going to look through them to satisfy myself that they are of that nature.

MS. BUCHWALD: Yes, your Honor. Within that I think we should include any earlier drafts of these regulations.

THE COURT: I accept that, pending Mr. Bass' demonstration that it is wrong.

Secondly, make a folder of materials that antedate the period up to the promulgation of the regulations that are here under review.

Third, make a folder of things that post-date.

I may not have covered everything in that arrangement. Have I left anything out that you possess?

MS. BUCHWALD: I believe that is it, but let me just make one check.

(Pause)

MS. BUCHWALD: No. As long as we also include within the intra-agencies' communications minutes of meetings, which are rather cursory. But I don't think there are any other categories --

THE COURT: Meetings of the Commissioner or his deputies with staff?

MS. BUCHWALD: Right.

THE COURT: All right. At the moment I will

include that.

MS. BUCHWALD: I believe that comprises all the categories of materials.

THE COURT: You think that covers it?

MS. BUCHWALD: I think so.

THE COURT: Before we go on, I want to hear from Mr. Bass.

The way it stands, Mr. Bass, subject to what I hear from you, I am disposed to give you everything except the intra-agencies' communications, which I will look at to satisfy myself that they are in that category, as I assume they will be, if Miss Buchwald says so.

What is your objection to that?

MR. BASS: First, your Honor, if I may, I would like to clarify with Miss Buchwald that the classification that has been set forth to the Court doesn't vary from what Mr. McNamara previously submitted.

I would like to ascertain that we are talking about the totality of documents which Mr. McNamara stated in his affidavit were obtained, and then he gave a general classification.

I want to be certain there has been no internal or self cutting down or specifying what documents come within this total picture.

THE COURT: You are going to have to come back Tuesday afternoon and you can hear the last few minutes of that day's trial, King Resources, and we will resolve this on Tuesday afternoon.

MS. BUCHWALD: Your Honor, I assure you we have not taken any material out.

MR. BASS: I don't mean taken.

THE COURT: You make the comparison between now and Tuesday. You are not going to stand here and do it on my time, and you will tell me Tuesday, "They left something out. The classifications are different" or they are not.

Assuming they are not, I want you to address yourself to the question whether I should give you the intra-agencies' communications which I believe you are not entitled to.

MR. BASS: Our position would be, your Honor, that both the intra-agencies' memoranda and the drafts are highly relevant here. We are talking about --

THE COURT: I am not talking about whether they are relevant. If you could get the things that Dr. Schmidt says **on his analyst's couch, it would be relevant, but you can't get them.**

See clip

The question is, are these things part of any

kind of record to which you are entitled on a review of an administrative agency's rule? And I think the answer is no. Is there any authority for a different view, that you can have intra-agencies' communications as part of that record?

MR. BASS: I would like an opportunity to get it for your Honor.

THE COURT: You were supposed to believe this. You were hollering that the Government didn't give you a big enough record for a couple of years now, and now they are giving you everything except the one category and you are not ready to tell me whether that is enough?

MR. BASS: I have all the briefs, but I don't remember, and in the months past I have not read them all --

THE COURT: All right. Tell me Tuesday afternoon, and you had better be ready to read me chapter and verse. We will stay longer Tuesday afternoon.

MR. BASS: If I know what your Honor wishes, I will have it all ready.

THE COURT: That is the only thing open. Unless Miss Buchwald is differently advised over the weekend, she is apparently ready to give you the rest.

Tell the people in your agencies that fighting about these details is not a fruitful use of their time or

mine.

I have read the Commissioner's latest affidavit, which I guess is over a year old now, dated February 1975 -- I'm sorry, February 1976. The reason I said '75 is that it has at its end a typographical error, "Sworn and subscribed to February 1975."

It is a twelve page affidavit filed February 20, 1976, and I think our record should show that the date at the end of it is a typographical error, yes?

MR. BASS: Yes, your Honor.

THE COURT: With your permission, I will change that. May I?

MR. BASS: Yes.

THE COURT: I have read through it and I find it somewhat persuasive. I want to ask this question:

Is there any evidence in the record now before the Court, or was there any evidence in the record, wherever that was, before the Commissioner, of therapeutic claims made by the vendors of these high-potency formulations?

I think the latest affidavit, unless I have skipped something, is devoid of any such assertions, and I want to know: Does the Commissioner make no claim that there was this kind of basis for his view or does he make such a claim?

I know he relies on socalled objective evidence of therapeutic intent, but that is not what I am asking about. I am asking whether he claims there was evidence of explicit claims of this nature by the vendors.

MR. BASS: Your Honor, I would respectfully submit, sir, on that question, that would be a question: Do all vendors make such claims or half of them or five percent of them?

We are talking about a regulation that will apply to all vendors and all sales of products about ten thousand units. If a certain number sell a product with a claim, I would respectfully submit that doesn't provide the basis that every other vendor who sells it is similarly bound.

THE COURT: There are varieties of factors, and I am trying to tick them off one at a time. I want to know if there is any such suggestion. If there is none, we don't reach your question, Mr. Bass. If the Commissioner claims there are explicit assertions of therapeutic purpose or intent, then I will listen to you about how many do and don't make such assertions.

Miss Buchwald?

MS. BUCHWALD: Your Honor, I believe at an earlier point in this litigation we had made reference to a

product produced by Solgar, one of Mr. Bass' clients. I believe at a later point he came in with an affidavit saying they had discontinued that label.

With respect to the promulgation of these regulations, and certainly as to Solgar, we withdraw any allegations that Mr. Bass' client was making a specific therapeutic claim.

I do not know, your Honor, of any evidence in the record making a specific reference to a label of a drug company making a therapeutic claim. However, I believe what the Commissioner is referring to generally, as he did when he promulgated this regulation, was a news letter of the American Academy of Pediatrics, which referred to the widespread promotion to the laity of these vitamins for therapeutic usage.

THE COURT: Let me give you a forecast of the work schedule. Tuesday we will meet and wrap up all the conversational problems and I will give you both a week to get in any additional supplemental memoranda, after which I will turn to this as immediately as my schedule permits and, within a week or two thereafter, decide it, for better or for worse.

One of the things I want you to have in mind for that final memorandum, both of you, is this question,

and I would like you both, by reference to these files of materials, to address it, tell me what there is in the administrative record that reflects therapeutic claims by the vendors or sponsors or others of these high potency vitamin formulations.

Mr. Bass, to put a point on our other question as to the record, if you satisfy yourself that Miss Buchwald delivered up everything that could arguably be the record, and if you get everything but the intra-agencies' communications, then I assume the only question that will be resolved adversely to your views will be the question with respect to those.

I will assume, unless you tell me otherwise on Tuesday, that you have no other complaint about a deficiency in the record. I am assuming on Tuesday you will tell me you ought to get the intra-agencies' things, and of course you will reserve that, OK?

Do you follow?

MR. BASS: Yes, sir.

THE COURT: If I am under a misapprehension with that formulation of the situation, you be sure to tell me that Tuesday.

MR. BASS: Yes, sir. Unless your Honor is referring to the examination of Commissioner Schmidt, and

I don't know if your Honor is treating that separately --

THE COURT: No. I don't want you treating it separately or together. I have brooded and brooded on that question and I believe I was wrong when I indicated that he ought to be called in to be examined. I believe it would be an unjustified kind of intrusion on the legislative or quasi-legislative responsibility of the Commissioner to haul him in here and have him examined as to why he delivered himself of these regulations, and I won't order it.

I believe what he has submitted as his recollection of his views is not a fit subject for examination and cross examination any more than I think we ought to haul a Congressman in here and cross examine him about whether he really meant what he said or whether he actually was bribed to pass the Sherman Act.

At least on this record, without being as general as that last remark might intimate, I see no justification for calling him in. I have read and reread the affidavits and I believe the question of the validity of these regulations must be thought out on the basis of that set of submissions by the Commissioner without further interrogation of him as if this were a trial of his actions now.

I realize that is debatable, but there is where I come out.

MR. BASS: May I raise this question with your Honor? I would submit that if your Honor, as your Honor has now ruled, ruled that we cannot examine the Commissioner, even with respect to the affidavit he has submitted, I think we are being put at a great disadvantage, because it is not a question merely of processes, but there are serious questions of time and bases in the light of the other proceeding, which your Honor recalls.

But the point I want to make is this. I am talking about the other vitamin regulation case. What I suggest is this: I will repeat my request to examine the Commissioner. I think that is very important, and I don't waive that.

If there is not going to be an examination, and if this proceeding ostensibly is going to be reviewed solely on the record at the time it was issued, I would submit this affidavit is not proper because it cannot add to or change anything that allegedly existed at the time this regulation was issued as to what the record was.

I would submit to your Honor that even though I don't waive the right to examine, which I think is very important in this particular proceeding, I think under those

circumstances we must at least strike the affidavit; it can't be part of the record.

THE COURT: I thought Judge Mansfield's opinion instructed the district judge to allow affidavits or hearing in some measure of informed discretion as to what seems necessary and appropriate, and the affidavit was put in, and to strike it from the record seems to be an exercise in futility.

see clip

If I sent it back to the Commissioner and you attacked his regulations, which is still in force, and has been during this leisurely briefing schedule, I assume he could come back with it now.

I won't strike it from the record. I think it is a responsible, debatable but relevant representation of what he believes was his reasoning processes underlying these regulations, and I will allow it to be attacked in any suitable way, but I will not strike it from the record.

MR. BASS: We can't attack it, sir, if we can't examine him.

THE COURT: If that is the only way you can attack it, you are helpless, I realize that. I don't think it is the law, and I don't think the Circuit made it the law, that administrative officials when issuing regulations, and maintaining the usual kind of record the

Administrative Procedure Act requires, can be hauled into court and cross examined as to why they issued the regulations.

You thought the record was incomplete. You persuaded the Circuit that some supplementation was necessary, and the question is what kind. And I conclude, after reading it and thinking about this, that the kind is the affidavit he submitted, and you may assail it in any suitable way. And if you think it is unassailable without cross examining him, then so be it and I will let you brief all of that.

I have one other question, which may be for briefing at some point, and then that will exhaust what I have for you.

In one of the paragraphs, number 9 of this affidavit, the Commissioner lists certain asserted public benefits that he says would follow from classifying these high potency vitamins as drugs and not as foods.

Without trying to recite them, there are certain powers to inspect and test which exist with respect to drugs but not food. My question is, I guess, twofold:

First, are these assertions correct as a matter of law? I assume they are, but I would like Mr. Bass to attack them, if they are not.

Second, are they pertinent to this proceeding? Is it a part of the justification for classifying these as drugs that it has these happy consequences? Does that fit as a matter of law within the statutory definition of a drug?

MR. BASS: Absolutely not, your Honor. That is one of the purposes of examination, for this reason: The statute as it exists today, for both foods and drugs, has extensive provisions, including criminal provisions, seizure provisions and injunction provisions against unsanitary conditions, unsafe products and dangerous products.

In other words, if a food is dangerous, unsafe or produced in unsanitary conditions, it is destroyed and the man is subjected to criminal proceedings, injunction or seizure.

There is no question about that.

THE COURT: My question was: Does that support his position that these ought to be defined as a drug?

MR. BASS: No, sir.

THE COURT: You think it does?

MS. BUCHWALD: Yes, sir.

THE COURT: That is a subject for briefing, because it is a legal question. I had some doubt, and I still have some doubt, whether it supports this categoriza-

tion, but I will read the briefs on it.

If, as Miss Buchwald is indicating, by jumping up and down, that she has already briefed it, the task will be to refer me back to that portion of the brief I have obviously forgotten, or to supplement it in any way you think appropriate. But I need the help of counsel on that question, and that is why I solicit it.

I have a similar question. There is a suggestion in Commissioner Schmidt's paragraph 10 that this is all in some way a waste of time because if it is not a drug then it will turn out to be a food additive and we will all be at the same place.

I am not sure whether it is my difficulty of comprehension or my failure to be persuaded that is the Commissioner's problem with respect to that paragraph, but I didn't follow it and it doesn't seem to me to add anything to his position in this case.

I don't know why he has it in there, Miss Buchwald. If it were not a drug and it might be a food additive doesn't seem to cut any ice. If he has not properly defined it as a drug and some other day he calls it a food additive, we will worry about that.

But why does he say, "Judg e, after all these years, you had better say it is a drug because otherwise

I will call it a food additive."

Explain that to me.

MS. BUCHWALD: I would think that the reason the paragraph was included was because of Mr. Bass' arguments that you do not have to be concerned about not classifying vitamins as drugs because they are foods and response to that doesn't really get Mr. Bass home free because it will be off the market anyway.

see clip

THE COURT: I want you to address yourself in your brief to the question whether that paragraph 10 as a legal matter or factual matter supports your position.

My untutored reaction to that paragraph was that it should be ignored or strucke out because it is really an anticipatory side issue rather than a really helpful supprt for what the Commissioner has done, and I want you to tell me in that many words whether it does or doesn't support what he has done and, if it does, how. If you say it doesn't, I will ignore it.

Mr. Bass, of course you do likewise. You have already indicated to me that it doesn't support him, and on that I tend to side with you at the moment. But I don't know where we come out in the end.

Those are all the things I wanted to talk to you about today. Are there any things you two want to talk

about before we adjourn for that final Tuesday meeting? Mr. Bass?

MR. BASS: No, your Honor. I don't have any other questions, sir.

THE COURT: Miss Buchwald?

MS. BUCHWALD: No, sir.

MR. BASS: At four-thirty, your Honor, on Tuesday?

THE COURT: No. I told the jury in the other case we would stay until five o'clock.

MR. BASS: Starting Wednesday morning I am going to be away for a week.

THE COURT: I wanted you to do the brief in that week.

MR. BASS: I have three days of depositions in Los Angeles.

THE COURT: You have somebody younger and healthier doing briefs. I would like it done in a week, for lots of reasons. If, after you think about it over the weekend, you need a little more time, I will certainly give sympathetic --

MR. BASS: Just a day or two after I get back from Los Angeles, your Honor.

THE COURT: You say your clients are in a

hurry, and I don't want to get you in trouble with your clients.

MR. BASS: You have seen my correspondence. We have been pushing, Judge, but within reason, and we didn't think it was that kind of thing which required making an issue out of it, and I never raised an issue with your Honor. We spoke with the Government and we worked along well, and it was not that serious if either one of us had a problem.

As far as resolving it, yes, we don't want the thing to go --

THE COURT: As soon as you get it done, we will get to it.

MR. BASS: Excuse me. There is one thing. In light of the position your Honor has indicated to us, I would like to tell your Honor, and tell counsel, I am going to submit to your Honor the new statute passed by Congress a few weeks ago, because in view of this turn I want this brought before the Court, I think perhaps now rather than as it would have been in a different proceeding.

THE COURT: What is the effect on our case of the new statute?

MR. BASS: It was basically intended to confirm Judge Friendly's decision on a number of questions,

including the drug definition.

It says that the Secretary may not classify a natural or synthetic vitamin or mineral or combination as a drug solely because it exceeds the level of potency which the Secretary determines is nutritionally rational or useful.

THE COURT: I take judicial notice of statutes, if somebody finds them for me. So you can put it before the Court. And I think it is good that you alerted Miss Buchwald. You, I assume, will cope with that new statute.

MS. BUCHWALD: There is no problem, your Honor.

THE COURT: See you Tuesday.

(An adjournment was taken to Tuesday, June 1, 1976 at 5.00 p.m.)

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TRANSCRIPT OF CONFERENCE DATED JUNE 1, 1976

U.S. DISTRICT COURT FILED SEP-9 1976 S.D. OF N.Y.

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF NEW YORK

- -x

NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

- against -

73 Civ. 3448

DAVID F. MATHEWS, et ano.,

Defendants.

- -x

B e f o r e:

HONORABLE MARVIN E. FRANKEL,

District Judge.

June 1, 1976 - 5:15 p.m.

A p p e a r a n c e s:

MILTON BASS, Esq.
Attorney for Plaintiffs

ROBERT B. FISKE, JR., Esq.
United States Attorney for the
Southern District of New York
BY: NAOMI REICE BUCHWALD, Esq.
Assistant United States Attorney

THE COURT: All right, Mr. Bass, Mrs. Buchwald, we had a couple of open questions and then anything else either of you or both of you want to say to wind up our oral discussion.

Mr. Bass, I think you were going to tell us the state of the authorities as you know them on whether you are entitled in this kind of proceeding to intra-agency communications, and specifically whether any authority exists for that position.

MR. BASS: Yes, your Honor.

There were two. I believe, your Honor, there was the intra-agency memoranda and also the drafts, I believe, were referred to, your Honor.

Your Honor, on this question of privilege with respect to those documents, thedrafts and memoranda, it is the plaintiffs' position, sir, that the claim, any claim of privilege would not be absolute. We would cite -- I have the Smith v. Federal Trade Commission case, your Honor, which is cited in our brief, that was previously submitted, of 403 Supp. 1000.

But it is also cited in a Supreme Court decision of United States v. Nixon, and other cases, sir, that would support the same proposition that this claim or any claim of this kind of privilege is not an absolute.

What we are dealing with is a balance of need against harm. Basically, that would be the equation --

THE COURT: Yes. What is your need?

MR. BASS: Our need, we say here, sir, that this case, if anything, would present very exceptional facts, as we view it, creating a need for obtaining any memoranda or drafts of this kind bearing upon the single issue before us other than --

THE COURT: Tell me about that. What are those singular needs?

MR. BASS: We are dealing with a situation where initially the defendant issued a regulation. In that regulation he said, "The basis by which I am calling this product a drug is that which I have laid down in my other regulation proceeding, to wit, that there is no usefulness as a food for this product in this potency, there is no food use."

That was the position he took and specifically in the very regulation that was published in the Federal Register he incorporated the reference to the other regulatory proceeding and the limits of potency set down there under Section 80, part 80 of the other regulation.

After doing that, we then have a discussion by Judge Friendly writing the opinion for the Court of Appeals

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striking down that premise.

We now have the defendant coming in and saying, "I have other reasons than I stated when I initially issued it." I will not burden the Court with all of them, but basically as I see them, your Honor, he is saying toxicity is an issue --

THE COURT: Whatever they are. I have read the material.

MR. BASS: And the question of food additive and what have you, you don't need it.

So we are saying, sir, that for any review of a record that existed then upon which this definition was constructed, it would seem that in this case, sir, there are more persuasive reasons where we have had this change.

In addition to the decision by Judge Friendly in the Court of Appeals, we have Congress enacting a statute in which it says even if it has no usefulness as a food, the Secretary should find that --

THE COURT: Look, I am not following you. Why does all of that or any of it give you a right to these intra-agency memos?

None of what you are saying is clear to me.

MR. BASS: The claimed right, your Honor, is for the Court and the plaintiff to have the record upon

which ostensibly the decision of the defendant was made, and I am claiming, your Honor, the fact here, which I think is very strong in terms of need as against the ordinary case, even, was this change that we have in the defendants' position.

THE COURT: In other words, you want intra-agency memos since Judge Mansfield wrote? Is that what you want?

MR. BASS: No, your Honor.

THE COURT: Before Judge Mansfield wrote?

MR. BASS: No, your Honor.

I want the documents which existed at the time the final regulation was issued, memos or drafts upon which this decision was made; not subsequent things, no, your Honor. That is the very point.

I want to see in the light of this changed position by the defendant whether it is so. There is a credibility question, your Honor.

THE COURT: You mean whether the reasons he is giving are his real reasons?

MR. BASS: Or post hoc. We have a really serious question. Is this a rationalization now as to what he said in the Federal Register?

THE COURT: How will those intra-agency memos

help you?

MR. BASS: I haven't seen them. I don't know.

THE COURT: Imagine them.

MR. BASS: I might find, for example, number one, they might not have any reasons that he claims that are at issue here.

THE COURT: Suppose that is right.

MR. BASS: Suppose toxicity was not involved, then I think there is a substantial question whether this was the basis of the issuance of the order, a proper basis, your Honor, as against any post hoc rationalization, your Honor. I think it is most relevant, your Honor.

THE COURT: All right. Do you want to speak to that?

MS. BUCHWALD: Only briefly, your Honor.

Mr. Bass' position is based on an assumption that the Commissioner has changed his rationalization of the issuance of the regulations, that in the first instance he promulgated the regulations on the other vitamin regulations before Judge Friendly. I think neither of those premises is accurate. There was no pinning of these regulations on the other ones, there was a reference to a numerical span in the other regulation, but there is a separate record which supports these regulations, separate

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reasons for them and they were treated separately, so I don't see any basis for this.

THE COURT: I probably won't give them to you, Mr. Bass.

Now let us assume, whether I do or not, is there anything else that you are claiming is not in this record that should be?

MR. BASS: Well, may I respectfully, your Honor, just for the record -- I feel that I would just like to bring to your Honor's attention a number of things on this subject, sir.

THE COURT: Go ahead.

MR. BASS: First, I just want to comment, sir, with respect to counsel's statement, my brief had specific reference to the Federal Register notice of August 2 --

THE COURT: That is all in the record. You can argue that.

MR. BASS: On this I do want to state for the record, your Honor, first, in answer to your Honor's question whether there is anything else, barring my ability to have an examination of the defendant, I don't know what is in there or not there. We are merely being told what is there, what will be given, sir. I have no way of answering the Court.

THE COURT: You mean you want to examine him about whether there is more in the file than he has told us?

MR. BASS: He has not told me anything, but a few papers have been given us, yes, your Honor. I don't know until I examine them.

THE COURT: He produced these 46 folders that are in this adjoining room.

MR. BASS: Yes, I know about that.

THE COURT: You want to cross-examine as to whether there is something he has not told us about that he has not produced?

MR. BASS: Correct, your Honor.

THE COURT: All right. I won't let you do that.

Do you realize that every agency head has to show up every time to swear that when he gives what he says is the record, it is true, because there is no case distinguishable from this one in that respect, so you would examine every rule-maker when he says, "This is the record." You want to cross-examine him in case he has hidden some papers from you, and that is what you are saying?

MR. BASS: Absolutely not.

THE COURT: Then why this point?

MR. BASS: Because this one has a tortured

history because we have not accepted the way it has gone, not the changes that have taken place here, your Honor, in the Federal Register publications as against the affidavits that have now been submitted. We cannot accept that. We are duty bound to inquire, your Honor. This has shifted.

I have engaged in rulemaking, I am engaged in regulations proceedings, and I do not make that request.

THE COURT: OK.

MR. BASS: It is only when this creates a situation when it is unique where this becomes an issue that we are compelled to raise that issue, your Honor.

I would like to note, your Honor, for the record, sir, if I may, on the question of the privilege which your Honor has just heard -- and I am not rearguing it, I just want to note for the record, sir, because I feel it is incumbent upon me to bring to the Court's attention -- it is our position that the issue of privilege has not properly been brought before the Court. It is our submission, sir, that in order for the defendant to raise such an issue, if he deems it warranted, the agency head must submit a proper affidavit with specific reference to the documents upon which this claim is being asserted and the reasons therefor. It cannot be done in

this general manner which has been now submitted by counsel for the defendant.

So I would like to note, sir, that our position is it is not properly presented before the Court for any kind of ruling by the Court.

On the other questions, your Honor, that I would like to touch, because they have come up in just in terms of the record, sir, for your consideration.

I would first respectfully ask, is your Honor going to have any discussion today as far as the basic issue? For example, toxicity which we were requested to brief as to whether or not --

THE COURT: No. If you have any more briefing to do on it, I am going to give you another week.

MR. BASS: I just want to know whether your Honor wants to discuss that, whether it is a proper definition, the toxicity.

THE COURT: No.

MR. BASS: What I would like to note for the record is as follows, your Honor:

I did ask, and your Honor denied, the request to examine on the completeness of the record. But I am also repeating our request to examine the defendant more fully, not only as to completeness of the record, but as to

the alleged basis for the definition in this case, sir, and very specifically the affidavits that have been submitted, affidavits 1 and 2.

This I would respectfully ask your Honor to consider. And I would like to note for the record, if I may, sir, only because we didn't have a record reference previously when we met on September 4 of 1975, when the defendant was directed to make a new affidavit that it did not include certain objectionable materials, such as post-dated material from the time of the issuance of the regulation, sir. I want to note that, because the question was raised at the end of February 1976 when the defendant submitted that.

At that time, your Honor, this was discussed and it was decided at that time in the Court's view at that time, on September 4, 1975, that in view of the issuance of the affidavit, the defendant waived any question of objecting to being examined as to the basis or what he did in arriving at that decision for the drug classification.

I recognize and understand your Honor on Friday had reconsidered and decided contrary to taking the deposition, but with all due respect, without imposing upon your Honor's time at this late hour, I would respectfully ask your Honor to consider our application even by way of

deposition. I don't want to impose upon the Court's time. I know the problem we are faced with on time, as your Honor is putting in these kind of late hours, that I would be happy --

THE COURT: Look, let's be straight. Don't reargue. It has nothing to do with my time, which is at the service of the litigants. It has to do with principles I perceive as being more importand, and I have tried to make clear to you that on rereading the authorities, Verdon and Park, Morgan and the rest, it seems to me to be quite beyond the path of hauling the Food and Drug Commissioner up here to be examined before either me or before a notary public, and it is not for the reason of the Court's time that I am denying your application in this respect.

MR. BASS: I just had wanted to add to that that as far as the convenience of the defendant, I was prepared to go to Maryland, at his office, to do it. I did wish to make that request of the Court, because as I mentioned earlier, sir, in this case, if ever there was a case where it is called for, sir, in view of all of the events that have transpired, an examination we feel, sir, is very important for any consideration as to the propriety of the statutory definition of this case, the adaptation

by the defendant of the alleged basis for the drug definition.

Your Honor had asked on Friday, sir, two questions, which if your Honor wishes I will defer the response to. That had to do with paragraphs 9 and 19 of the defendants' affidavit.

THE COURT: You may brief those.

MR. BASS: Thank you, sir.

MS. BUCHWALD: Your Honor directed on Friday that I consult with the Food and Drug Administration with respect to which documents the FDA would be prepared to show to the plaintiffs and to submit to the Court and I can report to your Honor that the FDA is prepared and willing to cooperate with your Honor on the matter of the so-called record materials as long as there is, as I believe there was, an understanding that they are producing this matter, this additional material, voluntarily and without any prejudice to their position that this material is not properly part of the record and that this does not become a precident for future proceedings.

The material that they are prepared to deliver to the other side is all the material in the files with the exception of the material withheld as being intra-agency privileged communications.

I have placed this material in folders

pursuant to your Honor's instruction. If I just briefly may recite them for the record, first, there is the supplemental record material number 1, and this material comprises all communications between the Food and Drug Administration and persons outside the agency from the time the regulation was proposed until the time the regulation was enacted. I have today two additional documents to deliver to the plaintiffs in addition to the material I delivered to them on Friday in that category.

THE COURT: As we go through these, let's get straight what you are reserving your position on, not that I think district court precedents are so fat and important. Would you claim that that particular category would normally not be a proper part of the record in this proceeding?

MS. BUCHWALD: Your Honor, not as to all the documents. There are some documents which I think are more properly considered part of the record and those concern comments which were solicited by the FDA from doctors concerning the exception that was included in the final regulations for Vitamin D products for special dietary use up to 1000 International Units for elderly persons who had absorption problems concerning Vitamin D. I think those matters might properly be part of the record.

There are, for example, a communication from an association called Vitaminerals Inc. and they wished additional time to submit comments and there is a response from the FDA or I should say it is a record of a telephonic response in which the FDA declined to officially extend the period they told Vitaminerals that they would have additional time, even though it is a communication between the FDA and the outside world. I do not think that that would normally be considered record material, but it is innocuous and we are turning it over.

THE COURT: I just wanted the record to show what you are making reservations about. That one doesn't seem very interesting to me.

All right. So supplemental record number 1 you are giving them. What is next?

MS. BUCHWALD: The next material is material which is the privileged intra-agency communications. These include intra-agency memoranda, prior drafts of the regulation and what are termed in FDA terms action memoranda. Those are initial steps --

THE COURT: All right. Let's understand about that, since Mr. Bass makes an important point of it. On that I propose to take that and look through it and satisfy myself that it is in the category that I have

excluded from the record here, and then I would propose, following a criminal law analogy, to seal it up and make it available for the Court of Appeals if review of that ruling is desired.

Is that agreeable with you?

MS. BUCHWALD: Yes, sir.

MR. BASS: Would it be possible for us to have some identification for any purposes of future review of the document in question by the defendant and the claimed harm, sir?

In other words, is it secret, something we can't disclose? I know some things naturally are. There are different categories of classification, your Honor, that come into play under the broad umbrella of privilege. I wonder if we could obtain from defendants some method in order to deal with it more specifically in terms of an identification of the document, whether it is a name they are trying to keep secret, or the content, what is the claimed harm or problem that is inherent.

THE COURT: By the way, you keep talking about privilege. I don't know whether privilege is an exhaustive rubber ring for this situation. I am just holding that these papers are no proper part of a record on which a Court should review informal rulemaking action by an

agency under the Administrative Procedure Act. I haven't assumed they are secret or --

MR. BASS: That is what I was directing myself to because of our Friday discussion with counsel.

THE COURT: They asserted that they don't think this is part of the record and that they shouldn't be obliged to turn it over.

Are they secret papers, Miss Buchwald?

MS. BUCHWALD: Your Honor, these are papers that the agency is not prepared to turn over. There is no claim of state secret, there is no claim of national secret. These are traditional --

THE COURT: I don't think that the memoranda that my law clerk writes to me should be classified top secret or even secret or even confidential, but I wouldn't turn them over to anybody, short of a lot of pressure that I haven't yet been put under, and I assume it's that kind of right that the Commissioner is invoking here rather than some military or intelligence or national security kind of classification.

You say that is about it, Miss Buchwald?

MS. BUCHWALD: That is the privilege that we are invoking.

MR. BASS: That is the right, your Honor, which

we think there has to be a determination of a balance here of any claimed harm here as against need.

THE COURT: I understand what you are saying. This is responsive to your getting up and asking what is the level of classification, and apparently there isn't any of those levels of the kind you are talking about. So we will seal it and let the Court of Appeals read it after I have read it, subject only to the possibility that when I read it I may have to call you back in and say one or another of these pieces of paper don't seem to me to fall within that privilege, as we will call it loosely. But if I don't find that I will order them sealed up and transmitted to the Court of Appeals.

MR. BASS: Your Honor, the position as I understand it now, I would just like to further bring to the attention of the Court what was in the case before the Second Circuit, I have their citations before the Second Circuit Court of Appeals, a Consumers' Union case against the Consumer Products Safety Commission, which I just think might have some relevance as to what was included in the record for that proceeding. In fact I think at that time it was even part of the FDA, the Consumer Products Safety Commission. I just wanted to call attention of the Court to the fact that these very documents we are discussing

here were included in that record, merely in terms of some change --

THE COURT: Give us the citation and I will look at it.

MR. BASS: Yes, your Honor, It is number 73-1617, Judge. I will get the cite.

THE COURT: I don't want to sit around while you keep hunting around.

MR. BASS: I will get the citation, your Honor.

THE COURT: Get it and phone it into us.

MR. BASS: Yes.

THE COURT: Miss Buchwald.

MS. BUCHWALD: Your Honor, I just note on that case I think there is a difference between what an agency chooses to make part of a record and what is technically part of the record which it must be compelled to produce as part of it.

If I just may go on, the next category of material which I have gathered is in a folder entitled "Correspondence Ante-Dating the Proposal of the Regulation." Once again it would be the position of the FDA that this is not part of the record of this regulation. I think that the interest of the FDA and any agency is to be sure that it need not scour its files for material which might

exist but which did not become part of its decision-making process on this particular regulation, it's the obligation of the agency to make a record and then try to sustain its action on that record. But we have no objection, in a spirit of accommodation, to turning this material over to the plaintiffs as well.

The next category of material is correspondence post-dating the regulation. The position on that is it is not part of the record, it's irrelevant. It occurred after the fact. Once again, we have no objection to turning it over.

The next category of material is additional medical articles. As I indicated before, some of these articles were included in the official record, some of them were not. We have no objection to turning them over.

The last category I have called miscellaneous for want of another category and it comprises essentially two things, some press releases with respect to the vitamin regulations and secondly some copies of the correspondence between a Dr. Robertson and the Kellogg Company of Battle Creek, Michigan, which was sent to the FDA.

THE COURT: All right. Let's agree on how you will handle your work physically. We have obtained from the

clerk's office the many folders that we understand to comprise what the agency has delivered as the record here and those should be available to both of you for your briefing work between now and next week. Suppose we re-deliver that to the clerk's office, where it will be available to both of you, unless you desire some other arrangement.

MS. BUCHWALD: Your Honor, we have submitted our memorandum on the record.

THE COURT: So you have no further briefing.

MS. BUCHWALD: We do not intend --

THE COURT: All right. Mr. Bass, does that suit you?

MR. BASS: Based upon what I have heard thus far, there may be no further discussion of the record needed, based upon what defendant is delivering. If I find after looking at the documents something further must be brought to the Court's attention I will do so. I am not going to burden the Court unnecessarily. If the documents are as they have been explained at this moment, then there may be nothing to add, your Honor, to what we have submitted thus far.

THE COURT: All right. In any event, this needs to be made clearly and unequivocally and certainly a

part of the record which I assume will go back to the Court of Appeals so that there will be no misunderstandings about anything being here that is not there, except for what we are excluding, which are those intra-agency papers. So you have read into the record what they are, Miss Buchwald. If you will hand them up to the clerk he will associate them with the other files, and that is the record, and then hand to me separately the intra-agency papers and I will read those and we will, as I say, attend to them in the fashion I have described.

Is there anything else that we need to talk about at this point?

MR. BASS: Nothing we have, your Honor.

MS. BUCHWALD: What day does your Honor wish the final briefs?

THE COURT: I have said a week. Mr. Bass indicated that he might need a little more than that. Is a week adequate, Mr. Bass?

MR. BASS: What I mentioned to your Honor about the week was simply I won't be back until Wednesday night. But that is if it is required. I don't know after looking at this record whether there is anything further needed, unless your Honor desires some further question.

THE COURT: I have invited you as this

jhas

conversation proceeded to brief one thing or another if you desire to and I am going to leave that to counsel. If you need any further briefs let's say you will get them in by the morning of June 9.

MR. BASS: If we meet at all, your Honor, could we make that the 11th, only because I won't be in New York until the 10th.

THE COURT: All right, get it in by the 11th.

MR. BASS: If we need it. If we don't need it we will let your office know.

THE COURT: If you don't need any drop us a note saying you don't need any further briefs and if we can get to the case sooner we will.

All right. Thank you.

- - -

I (We) hereby certify that the foregoing is a true and accurate transcript, to the best of my (our) skill and ability, from my (our) stenographic notes of this proceeding.

Official Court Reporter
U. S. District Court

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

- x

NATIONAL NUTRITIONAL FOODS ASSOCIATION and SOLGAR CO., INC.,

Plaintiffs,

-against-

DAVID F. MATHEWS, Secretary of Health, Education and Welfare and ALEXANDER M. SCHMIDT, Commissioner of Food and Drugs,

Defendants.

- x

73 Civ. 3348

OPINION

4/4/73

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FRANKEL, D.J.

This case, on remand now "to conduct an Overton-type hearing," National Nutritional Foods Ass'n v. Weinberger, 512 F.2d 688, 703 (2d Cir.), cert. denied sub nom. National Nutritional Foods Ass'n v. Mathews, 423 U.S. 825 (1975),

was brought in August of 1973, seeking declaratory and injunctive relief against regulations of the Food and Drug Administration requiring that preparations of Vitamins A and D in excess of 10,000 IU (international units) per dosage unit and 400 IU per dosage unit, respectively, be restricted to prescription sale, and that such vitamins be labelled accordingly, 21 C.F.R. §§ 250.109 and 250.110 (1976). Plaintiff's motion for a preliminary injunction was denied on September 25, 1973, 366 F. Supp. 1341 (S.D.N.Y.), aff'd, 491 F.2d 845 (2d Cir. 1973), and the regulations became effective on October 1, 1973. Defendants' subsequent motion for summary judgment was granted, 376 F. Supp. 142 (S.D.N.Y. 1974), a decision which has been, as noted, vacated and remanded. Moving at a rather leisurely pace, the parties have now submitted additional materials and arguments, supplementing those already before the court from the two previous motions. For the reasons hereinafter outlined, the regulations are upheld as not "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," 5 U.S.C. § 706(2)(A), and the complaint will be dismissed.

I.

A couple of procedural issues are presented at the threshold. Plaintiffs argue, on principle and under the terms of the mandate of the Court of Appeals, that Commissioner

Schmidt should be subjected to cross-examination concerning the grounds on which he classified high-potency Vitamins A and D products as "drugs." In addition, there is a question as to the scope of the "record" upon which the court should make its determination. On both subjects, the court is in disagreement with plaintiffs' position.

A. "The great developer is responsibility."[1]

That familiar bit of Brandeis wisdom remains vital. Time and travail, even Watergates, should and must not close it from our minds. There may be imaginable occasions when judges ought rightly to summon high agency officials to undergo cross-examination about the legislative premises underlying their formally published rules. There may even be occasions when legislators could be commanded to do likewise. But the instances would surely be rare, marked by circumstances of some extraordinary character.

An Overton-type hearing is not an open invitation, much less a direction, to cast aside this familiar learning, recognized for administrative decisionmaking since United States v. Morgan, 313 U.S. 409, 422 (1941). The case for which the present "hearing" is named recognizes, first, the limited circumstances in which the administrator's mind may be probed by examination, and,

second, the discretionary nature of such an examination even when the exceptional circumstances have been met. Citizens to Preserve Overton Park, Inc. v. Volpe, 401 U.S. 402, 420-21 (1971); see also Camp v. Pitts, 411 U.S. 138, 142-43 (1973).[2] The Court of Appeals demanded no more in this case, 512 F.2d at 703 ("including such affidavits or testimony as to the Commissioner's reasoning as the court deems necessary").

In this light, the court requested, and received an affidavit from the Commissioner. Plaintiffs have pitched various arguments against the affidavit, and these have been considered. Their contention that they are entitled to more - entitled to cross-examine the Commissioner as well - is unfounded as a matter of law, and unsupported, insofar as it is a matter of discretion, by any demonstration of great necessity. The niceties of the Administrative Procedure Act were nowhere neglected in this case. The indicia of due notice, full deliberation, and general regularity are all present. There is nothing so irregular or peculiar as to justify the expedient of having the agency head grilled on the witness stand about what he thought he knew, what he now thinks he believes, and how he may have reasoned, in making the mixed judgments of fact, policy, and law which underlay the decision to define these high-potency vitamin pills as "drugs."

B. The question about the "record" is narrower, and still less gripping. The record originally before this court consisted of the materials produced by the "notice and comment" provisions of the Administrative Procedure Act - to wit: (1) the official notices by the F.D.A., with cited reference materials incorporated by reference; (2) the voluminous comments, some 45 folders full, received in response; and (3) the promulgated rules and their published explanations. The agency contends that this satisfies the proper definition of the record.[3] Even so, in a spirit of accommodation, the Commissioner has now placed before the plaintiffs and the court other material found in his files, namely, correspondence with third parties antedating the proposed regulations and postdating the final regulations, a few additional medical articles, and five other "miscellaneous" pieces of paper. The only items withheld from plaintiffs are a sheaf of some two dozen papers, all consisting of internal F.D.A. memoranda or proposed drafts of the original notice.[4]

Plaintiffs press for these papers as well, contending that they should be treated as a part of the agency record.[5] The contention is not persuasive. What plaintiffs seek are presumptively privileged documents, whose privacy is left untouched by the Freedom of Information Act's exemption from disclosure for

"inter-agency or intra-agency memorandums or letters which would not be available by law to a party other than an agency in litigation with the agency," 5 U.S.C. §552(b)(5). There is no reason to think that the need to compile a "record" for a judicial review proceeding makes this limitation inapplicable, especially in light of the general proscription against probing the mind of the administrator. And there is, in any event, no showing of justification for the kind of invasion plaintiffs propose.

In short, the material now before the court and the agency, supplemented, as it is, by the voluntary production by defendants of all non-privileged documents, has given plaintiffs all, and probably more, than they are entitled to have as the administrative record for judicial review of informal agency rulemaking. See Rodway v. United States Dept. of Agriculture, 514 F.2d 809, 817 (D.C. Cir. 1975); Phillips Petroleum Co. v. F.P.C., 475 F.2d 842, 850 (10th Cir. 1973), cert. denied, 414 U.S. 1146 (1974); City of Chicago v. F.P.C., 458 F.2d 731, 740-41 n.45 (D.C. Cir. 1971), cert. denied, 405 U.S. 1074 (1972); Automotive Parts & Accessories Ass'n v. Boyd, 407 F.2d 330, 336 (D.C. Cir. 1968); see also National Petroleum Refiners Ass'n v. F.T.C., 392 F. Supp. 1052, 1053 (D.D.C. 1974).[6]

II.

The central substantive question to be examined on this remand is whether or not the Commissioner's classification of high-dosage preparations of Vitamins A and D as "drugs" within the Food and Drug Act's statutory definition, §201(g)(1), 21 U.S.C. §321(g)(1), was "arbitrary, capricious or otherwise not in accordance with law." The start of our inquiry, the statutory definition of a drug, reads, to the extent relevant:

> "The term 'drug' means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals * * *."

With respect to whether the record supports the classification of high-dosage preparations of Vitamins A and D as drugs, the focus in these proceedings has been on subsections (A) and (B) of the definition.

Respecting subsection (A), both sides recognize that the intervening decision in National Nutritional Foods Ass'n v. F.D.A., 504 F.2d 761, 788-89 (2d Cir. 1974), cert. denied, 423 U.S. 827 (1975) precludes any simple reliance on the presence of an item in the official United

States Pharmacopoeia or the official National Formulary: "the argument would prove too much, for it would lead to the conclusion that all vitamin and mineral preparations even within the limits are drugs * * *." Not accepting this as the end of the matter, the Commissioner, in his affidavit, counters by arguing:

> "Unlike most articles recognized in the U.S. Pharmacopeia and the National Formulary, which are included because of therapeutic usage, vitamins A and D are specifically recognized in the U.S.P. and N.F. for prophylactic (food) usage as well as for therapeutic (drug) usage. In my judgment, while the Act provides that an article is deemed to be a drug if 'recognized' in the U.S.P. or N.F., a vitamin preparation should nevertheless not be classified as a drug on this basis with respect to a usage which is specifically recognized by these compendia to be a prophylactic (food) usage. Consistent with this principle, the vitamin preparations subject to the regulations exceed the levels of potency recognized as 'prophylactic' in the United States Pharmacopeia and National Formulary * * *." (Emphasis in original)

The argument has weight, for otherwise it is unclear what force would remain of subsection (A) of the definition. It appears, however, to be a new thesis, not evident to justify the regulations as originally promulgated. If this were all the Commissioner had, his position could be highly vulnerable. It would appear to suffer the fatal disorder of post hoc rationalization. Cf. National Nutritional Foods Ass'n v. FDA, 504 F.2d at 788-89. However, the court finds enough that is valid and substantial to sustain the agency.

The bulk of the contentions concerning the validity vel non of the decision to classify the affected preparations as drugs has focused on subsection (B) of the definition. The course of decision is guided by the decision of the Court of Appeals, which stated, 512 F.2d at 703:

> "Upon adoption of the regulations the Commissioner stated that since there was no evidence that the higher dosage levels were used for nutritional purposes except for use of Vitamin D by a limited number of persons with poor Vitamin D absorption needing up to 1,000 IU daily, they 'are therefore appropriate only for therapeutic purposes and thus properly classed as drugs.' As Judge Friendly said, 'demonstrated uselessness as a food for most people' would not automatically establish that the higher levels qualify as a 'drug' within the definition in §201(g)(1). The statute requires a finding of intent that a product be used for therapeutic purposes, and the Commissioner made no such finding. However, in his earlier statement proposing the regulations here under review the Commissioner stated that 'there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders.' This statement indicates that the Commissioner, upon promulgating the regulations, may not have fully stated his reasons for classifying the higher levels as drugs. It is conceivable, for instance, that the Commissioner had before him information demonstrating that the higher dosage forms were used almost exclusively for therapeutic purposes. Measuring intent on an objective basis, as it must be, he may have concluded that in view of the extremely small percentage used for nutritional purposes

> Vitamins A and D at higher dosage levels were intended for use in the 'cure, mitigation, prevention or treatment of disease.' In that case his action could hardly be arbitrary or capricious and the regulations could, consistently with NNFA v. FDA, be upheld."

Proceeding in this light, an examination of the record, together with the affidavit of Commissioner Schmidt, demonstrates that the classification of high-potency preparations of Vitamins A and D as drugs was not "arbitrary or capricious," and, accordingly, must be upheld.

In the first place, the Commissioner found "on the basis of all the available evidence, that vitamins between the upper and lower limits as specified in §80.1 are adequate for all known nutritional needs for normal individuals * * *." He further noted that "[n]o evidence was submitted in the comments to establish a food or nutritional use of vitamin A or vitamin D at higher levels, except for a limited number of persons with poor vitamin D absorption who need up to 1000 IU of this vitamin [and for whom an exception is made in the regulation]." After an examination of the record, these findings appear neither arbitrary nor capricious. It was, to be sure, noted in National Nutritional Foods Ass'n v. FDA, 504 F.2d at 791, quoting the NAS 1974 edition of Recommended Dietary Allowances, that

> "RDA are estimates of 'acceptable daily nutrient intakes' in the sense that, although the needs of most individuals will be less than the RDA standard, there may be a small number who require more. . . . It is not possible to be more explicit about the relationship between RDA and the requirements of an individual; thus, it is only within the framework of statistical probability that RDA can be used legitimately and meaningfully."

However, as a matter of sufficient "statistical probability," the Commissioner's conclusions withstand plaintiffs' assault. Meaningful studies, relied upon in the record, indicate that, at least for vitamins A and D, the RDA levels are adequate for virtually all healthy people, and "[e]xcept in situations of impaired fat absorption * * *should not be exceeded," Oliver, Chronic Vitamin A Intoxication, 95 Am. J. Dis. Child 57, 67 (1958).[7]

Moreover, as the Commissioner stated in the supporting commentary to the regulations, the record contains no affirmative evidence of nutritional usefulness for anyone above the levels dealt with in the regulations, while the evidence does reveal extensive therapeutic uses for these high-potency preparations. Furthermore, the methods of distributing the products makes clear they are addressed to a mass market, not to the rare few with exceptional nutritional needs.

In sum, the record supports a finding that the high-potency preparations in question have no demonstrated usage as a food, at least for all but an "extremely small percentage"

of the population, above the levels established in the regulations. While, in light of National Nutritional Foods Ass'n v. FDA, 504 F.2d at 790-91, this factor alone may not be sufficient to save the regulations from attack, it is certainly a relevant and important datum in the Commissioner's favor. As the Commissioner stated in his affidavit, "much more than 'demonstrated uselessness as a food for most people' is involved in the drug determination in the present vitamin A and D regulations. * * * These high potency vitamin A and D preparations provide excessive amounts of the vitamins which are useless as a food for virtually anyone * * *."

It is noted, further, in examining "objective intent," that the Commissioner's support of his regulations does not stop with simply a showing of uselessness as a food for virtually all people. The Commissioner, in his earlier statement proposing the regulations, stated that "there is widespread promotion to the laity of excessive quantities of these vitamins for prophylaxis and treatment of a variety of diseases and disorders." This statement, while it probably is supportable simply on the basis of the Commissioner's own knowledge from experience.

Consumers Union of United States, Inc. v. Consumer Product Safety Comm. 491 F.2d 810, 812 (2d Cir 1974); Chemical Leaman Tank Lines, Inc. v. United States, 368 F. Supp. 925, 940

(D. Del. 1973), also finds support in the record material before the Commissioner when he made his decision. Articles, both in the medical and the popular press, have advocated the taking of Vitamins A and D in large quantities to cure diverse ills from acne to night-blindness. See, e.g., American Academy of Pediatrics, Newsletter, Vol. 23, No. 9 (June 1, 1972) ["The use of high doses of vitamin A (25,000 to 50,000 units/day) has been recommended by Adelle Davis in the lay press, on radio, and on television."] The finding of widespread promotion of high-dosage preparations in the treatment and prevention of disease is also supported, as a matter of rational inference,[8] by the vast numbers of comments received on the proposed regulation from people who desire to continue the taking of the high-potency vitamin preparations for, inter alia, hay fever and prevention of colds or infection,[9] as well as by the scholarly literature reporting similar widespread beliefs among the laity. See, e.g., Gerber, Raab & Sobel, Vitamin A Poisoning in Adults, 1954 Am. J. of Med. 729.[10]

This public promotion of high-dosage quantities of Vitamins A and D for the "cure, mitigation, treatment, [and] prevention" of a variety of ailments, when coupled with the fact that there exists little, if any, evidence of known nutritional requirements beyond the limits imposed in the regulations, justifies the conclusion that the classification as drugs of high-dosage preparations of Vitamins A and D

is neither arbitrary nor capricious, and must be sustained.

Once classified as drugs, these preparations may be denominated prescription drugs, 21 U.S.C. §353(b), in view of the substantial evidence of their possible toxicity in high-dosage quantities. National Nutritional Foods Ass'n v. Weinberger, 512 F.2d at 704. The remaining issues have already been disposed of in the prior proceedings in this case. An examination of the record, the affidavits, and the parties' arguments leads to a ruling that the promulgated regulations are not arbitrary, capricious, or otherwise subject to attack.

The complaint is dismissed. So ordered.

Dated, New York, New York
July 2, 1976

MARVIN E. FRANKEL

U.S.D.J.

FOOTNOTES:

1. Letter from Louis D. Brandeis to Robert W. Bruce, February 25, 1922, in Richberg, The Industrial Liberalism of Justice Brandeis, 31 Colum L. Rev. 1094, 1099 (1931).

2. See Pedersen, Formal Records and Informal Rulemaking, 85 Yale L.J. 38, 50 (1975); cf. Dunlop v. Bachowski, 421 U.S. 560, 565-66 n.6 (1975).

3. A "Supplemental Record #1" has been produced, consisting of a few additional letters and a couple of memoranda to files which defendants acknowledge probably should be considered a part of the record.

4. These have been examined by the court to ascertain whether they are fairly and accurately characterized as intra-agency communications and prior drafts. The court so finds. Government counsel will be expected, of course, to keep the documents submitted in camera for further inspection, if necessary, by the Court of Appeals.

5. Plaintiffs have also demanded discovery to see what else may exist in the agency files. The demand has been denied.

6. The bulk of the legal writing views the record in review of informal rulemaking as consisting of the agency's initial proposal, with supporting material, the comments received, and the final rule. See Pedersen, supra, 85 Yale L.J. at 64-66, 75-76; Wright, The Courts and the Rulemaking Process: The Limits of Judicial Review, 59 Cornell L. Rev. 375, 395 (1974); Hamilton, Procedures for the Adoption of Rules of General Applicability: The Need for Procedural Innovation in Administrative Rulemaking, 60 Calif. L. Rev. 1276, 1333-34, 1336 (1972); Note, Judicial Review of the Facts in Informal Rulemaking: A Proposed Standard, 84 Yale L.J. 1750, 1752-53 n.16 (1975). A recommendation of the Administrative Conference of the United States is a bit broader, 1 C.F.R. §305.74-4(c)(1)(1976). The material submitted by defendants fulfills the broader view, with the exception of "factual information not included in the foregoing * * * that is proffered by the agency as pertinent to the rule." As for this, which would smack of post hoc rationalization if it were submitted, the plaintiffs do not contend for it. See also Pedersen, supra, at 65.

7. See National Academy of Sciences, Food and Nutritional Board, National Research Council, Recommended Dietary Allowances ("long experience has shown that 400 IU/day are sufficient to meet the [Vitamin D] requirements of practically all healthy individuals, assuming no exposure to ultraviolet light"). See also AMA Drug Evaluations, 2d ed. (1973) at 153-55:

> "The Recommended Dietary Allowances (RDA) for individual vitamins established by the Food and Nutrition Board of the National Research Council provide authoritative information to assistthe physician in evaluating the formulas of multivitamin preparations * * *. These allowances, shown in Table 1, represent amounts that will maintain good nutrition in practically all healthy persons, and are usually considerably greater than the Minimum Daily Requirements (MDR) established by the Food and Drug Administration for labeling purposes * * *.
>
> "It is often assumed that a dietary intake of less than the Recommended Dietary Allowance by itself indicates substandard nutrition or even a deficiency. There is no justification for such a belief. In the 1968 edition of its publication, Recommended Dietary Allowances, the Food and Nutrition Board states:
>
> > ' * * * Since the RDA are designed to be adequate for practically all of the population of the United States, they allow a margin of safety for individual variations.'" (Emphasis added).

8. Cf. United States v. Allegheny-Ludlum Steel Corp., 406 U.S. 742, 749 (1972); Gaines v. Martinez, 353 F. Supp. 780, 790 (N.D.Tex. 1972).

9. Selected comments, from two folders (#28 and #35) are reprinted in an Appendix, infra.

10. This article noted not only that "[l]arge doses of vitamin A are used in the treatment of skin, eye, renal, gynecologic and ear disorders as well as the common cold," but also that "[s]elf-medication with vitamin concentrates containing large does of vitamin A is a common occurrence due to the general belief by the laity that vitamins improve health and increase resistance to infection." Id at 737, 744.

APPENDIX

Folder # 28

Letter, Mrs. Leslie W. Boodry, Feb. 5, 1973: "For over 40 years I have had food allergy problems. Having studied Adelle Davis's books and thus supplementing my diet with one of the B vitamins, namely Pantothenic Acid, I have been able to eat without any reactions or side effects, all of the many foods which previously were not tolerated by my body."

Letter, Herbert Shapiro, Feb. 4, 1973: "I have been successfully using vitamin A (25,000 units per day) for the past 10 years. 10 years ago I was a very sick person - one infection after another and I believe the vitamin A & C has helped greatly."

Letter, Marion Cotton Whitcher, Jan. 29, 1973: "Why do you suppose 7,000,000 copies of Adelle Davis' book have been sold? Why do you suppose health food stores are springing up all over the country? * * * [B]ecause Adelle's suggestions work, that's why. People use vitamins and natural foods and their health improves. The ill become well often to the surprise of their doctors."

Letter, Corry Duda, Jan. 31, 1973: "From personal experience, a friend had terrible menstrual cramps every month for years; sometimes passing out from the pain. * * * We read 'Lets Get Well' by Adelle Davis and tried for a month calcium tablets and 25,000 units of Vitamin D daily. Not only did all her pain subside but she did not have the slightest toxic sympton [sic]."

Letter, Brenda Walton, Feb 5, 1973: "there are so many more of us who depend on these supplements as daily insurance of sustaining good health and combating disease. * * *"

> "The endless wonders food supplements have performed (such as curing numerous serious illnesses, sustaining health . . . & etc.) far outweigh the temporary harm they may have caused to a few thoughtless users."

Letter, Jan Meridith, Feb. 2, 1973: "My elderly Mother after two broken hips and several crushed vertebra is able to walk again due to natural vitamins. My diabetic Father is now able to live, and eat a rather normal diet without medication due to his intake of multiple vitamins."

Letter, Mrs. Joyce A. Douglas, Feb. 6, 1973: "I have taken as much as 300,000 units of A a day for two months * * *. This I did to rid myself of an infection I had for 9 years, on and off. * * * I have given my children 50,000 units of A a day for a few days for colds and flu. * * *"

" * * * I am a follower of Adelle Davis. And if the people of the FDA would read her books and practice what she says they would laugh at this limit on A & D they want."

Letter, Pearl Stanford, Feb. 1, 1973: "There is a growing number of people in America who are becoming informed through T.V., Radio, and Scientific publications, and there are organizations who work to make scientific facts available to the public. Long before the Vitamins were known or named, Cod Liver Oil was known for its healing powers."

Letter, Mrs. Susan Gilson, Jan. 31, 1973: "If my children are ill, I have given them 25,000 units of vitamin A for a short time with vitamin E to help them combat the infection."

Letter, Larah H. Waszink, Feb. 8, 1973: "In the United States with competent advice from M.D.'s and the great nutritionist Adelle Davis I got rid of the arthritis with large doses of A,D,C,B,E, etc."

Letter, Mr. & Mrs. Tom F. Marunich, undated: "Some of the attributes of Vitamin A are, - clearing up ear aches, sore throats, vaginal infections, strengthening ones vision, clears acne, helps remove warts, gum infections, applying this vitamin to wounds and burns helps heal unbelievably fast not to mention other things."

"Some of the attributes of vitamin D are, - helping to relieve menstrual cramps, * * * relieves nervousness, irritability * * *."

Letter, Mrs. Edward Button, Feb. 5, 1973: "If it wasn't for Vitamin A my face would have been covered with warts. Doctors wanted to give me a strong medicine (which is known to destroy the bloodcells) but instead I found an article saying that Vitamin A had been known to dissolve warts."

Letter, Mrs. Frances Hale, Feb. 9, 1973: "Adelle Davis on p. 372 of 'Let's Get Well' says, 'When 300,000 units of vitamins A and 1,000 milligrams of vitamins C were given daily for three to six months to 218 cases of inoperable cancer, the malignancies regressed in size or remained stationary.'"

" * * * I then read Dan Dale Alexander's book on 'Arthritis and Common Sense.' I started taking codliver oil.

I took bottles of the stuff, I also took over doses of a multi-vitamin preparation."

Folder # 35

Quote in a letter, from Virginia Elenbaas, December 15, 1972, ostensibly from the Grand Rapids Press; "Heavy promotion of both Vitamins A and D for the treatment of acne, night blindness . . . neither is proven effective for these conditions in well nourished people."

Letter, signature cut off in copy, Jan. 3, 1973; "I myself have taken 100,000 I.U. of vitamin A every day for months and my problems are cleared up in many ways. * * **

" * * * And I may say I have proved that taking large amounts of Natural food supplements has kept me from having colds, flu and various different ailments that people come in to my store with."

Letter, Martha Bevis, Jan. 22, 1973; "Our 5 year old was born also with asthma and an eye problem which has been helped with vitamins. I give him a minimum of 25,000 units of A and 2,500 of D every day. Then every few months I give him 50,000 units a day for a while. The pediatrician I did have said vitamins couldn't possibly help anyone. My answer to him was 'If you will look at my bills, you will see that I'm not coming in with sick children anymore, because I don't have sick children since we started on vitamins.'"

" * * * Drs. Cheraskin and Ringsdorf at the University of Alabama have written of tremendous success treating all kinds of diseases through nutrition and vitamins . . . 'New Hope for Incurable Diseases.'"

Letter, Mrs. Helen Bibby, Feb. 8, 1973; "I have been taking massive doses of Vitamin A and D for years. (In excess of 125,000 USP Units of A & 2500 USP [units] of D.) I do not wear glasses. I have not been sick for over 5 years. I have not seen a doctor for any illness * * *."

Letter, Mrs. W. C. Jacobs, undated; "Why prevent the Citizens of America from improving their health? From preventing Cancer - or its return, if you've had it?"

Letter, Mrs. Frank Brogan, Feb. 16, 1973; "This [these regulations] means for me the return of backaches, abdominal cramps, or lack of energy in the evening, the inability to kick colds, flu, etc."

Letter, Alandette Fitzgerald, Feb. 2, 1973: "Quite sometime ago, I had an infection I could not shake on my own, so I was constantly relying on anti-biotics. This was not only depressing, but the cost was ridiculous. Then I read about Dr. Linus Pauling's study on vitamin C. After trying his recommended levels of vitamin C, I knew he wasn't awarded the Nobel prize for nothing! I take other vitamins now and so does my family. Needless to say, we are enjoying better health."

Letter, Hester Robinson, Feb. 7, 1973: "Years and years ago a nutritionist (I believe it was E. V. McCollum) demonstrated the value of large amounts of Vitamin A in delaying the aging process. I cured a rash with 100,000 units of Vitamin A daily."

Letter, Margaret Melcher, Jan. 25, 1973: "I have for four years taken 30,000 units a day of Vitamin A and found it instrumental in doing away with my allergies."

Letter, Macklin W. Schabitzer, Dec. 16, 1972: "I am 60 years old and I have been taking one (occasionally two) therapeutic multi-vitamin capsules every day for the past 10 years."

585a

Family Safety Article

Vitamin A: The See Vitamin

by Adelle Davis

IF YOU EAT an average American diet, work in either bright or dim light or watch television for several hours daily, you are probably headed for trouble. The next time you get behind the wheel of a car after dark, you're likely to be a first-class candidate for night blindness – a widespread malady that is caused by an equally widespread deficiency of vitamin A.

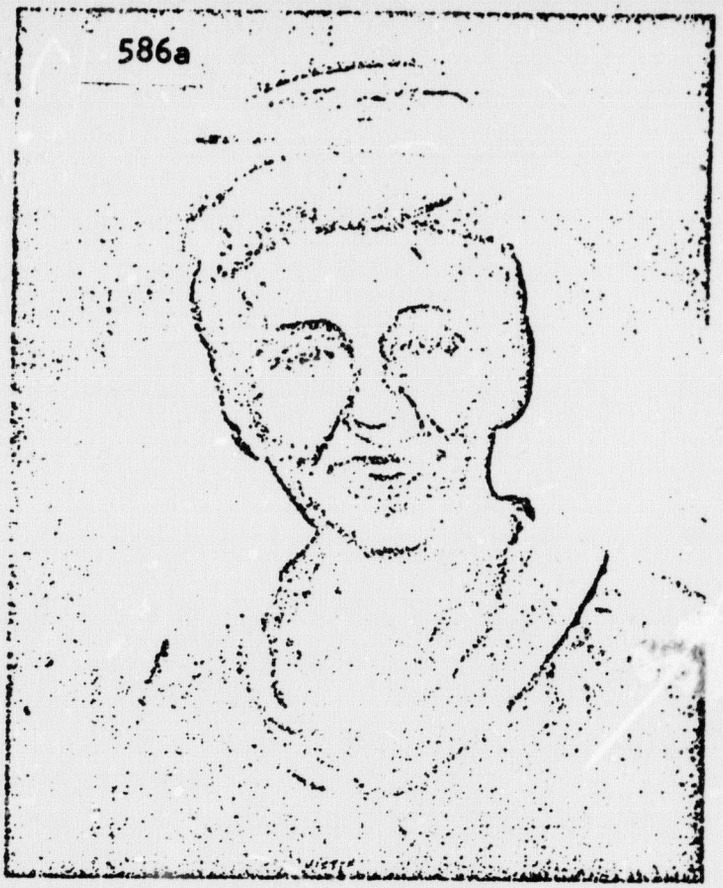
According to a conservative estimate based on a U.S. Department of Agriculture survey, roughly 50 million Americans lack sufficient vitamin A. Furthermore, this deficiency becomes more common each year, largely because vitamin A is destroyed by the nitrates in our foods grown with chemical fertilizers.

Now consider that traffic fatalities are 2½ times greater at night than in the daytime. What we eat—or fail to eat—can affect almost everything we do in life. As far as car accidents occurring at night is concerned, your nutrition can even spell the difference between life and death.

Several years ago, a study was conducted at Randolph Air Base in Texas, where an alarming number of accidents were occurring on take-offs. Faulty nutrition proved to be the culprit, and after the pilots were given nourishing pre-take-off meals, such accidents were virtually eliminated.

A popular myth has it that the way to see in the dark and decrease our nighttime traffic accidents is by eating large amounts of carrots. The origin of this belief appears to go back to World War II, when the British discovered radar. The first RAF pilot who used it shot down so many night bombers he became known as "Cat's Eye" Cunningham. Fearing that the Germans might suspect they had a secret weapon, British agents in neutral countries spread rumors that credited Cat's Eye's record to eating carrots and the prevention of night blindness. The story goes that the Germans promptly fed their pilots huge amounts of carrots but without success.

You can suspect that you have a vitamin-A deficiency if, while you are driving at night, you have trouble distinguishing objects from their backgrounds, are sensitive to glare, and if it takes some time to regain your vision after passing the headlights of an on-coming car. For example, one study of 162 drivers involved in night accidents showed that 62 per cent suffered from night blindness caused by glare. Studies have shown that at 50 mph, the "average" driver travels 73 feet *totally blinded* by the headlights after meeting an on-coming car. If your vitamin-A intake were extremely low, you could be blinded while driving twice or three times this distance. Another study of 321



About the Author

Adelle Davis, one of the country's best-known nutritionists, graduated from the University of California at Berkeley and received a Master of Science degree in biochemistry from the University of Southern California Medical School.

After a long and distinguished career as a consulting nutritionist, she now devotes all her time to writing and lecturing. She is the author of a number of best-selling books including *Let's Eat Right to Keep Fit, Let's Cook It Right, Let's Get Well* and *Let's Have Healthy Children*, which was just published in an enlarged and completely revised edition.

accident-repeaters revealed that all rated dangerously low in night vision, or in the amount of vitamin A available to their eyes; 75 per cent of their accidents happened after dark.

Vitamin-A deficiency comes in a wide variety of sizes. With a mild deficiency you would probably consider your vision to be normal, yet you would see better in the daytime than at night. If your deficiency were somewhat more severe, your eyes might feel tired after slight use, such as watching television. As the deficiency becomes more acute, you would probably suffer from headaches, from burning, itching and inflamed eyelids, and from actual pain in the eyeballs themselves.

The amount of vitamin A needed varies with your activities. People who work in bright or dim light use up more of this vitamin than those who work in moderate light. Miners and welders, typists and bookkeepers, engineering draftsmen and commercial photographers all need generous amounts—as do people who sew, read, watch television, and write books and articles.

Vitamin A, a colorless substance found in animal foods, is formed in the bodies of animals and humans alike from a yellow pigment, carotene, which occurs in all green and yellow vegetables. Carotene is supplied not only by carrots, apricots, squash and yams, but also by green vegetables, green pasture crops and seaweeds. The brighter the green or yellow, the more carotene the food contains. The colorless vitamin A itself, already formed from carotene, can be obtained from liver and fish-liver oils; both carotene and vitamin A proper are supplied by egg yolks, butter and cream.

In preventing night blindness, this amazing vitamin works much like film in a camera. A substance containing vitamin A, known as visual purple, forms in the eyes. When light reaches the eyes, it breaks down some of the visual purple, thereby causing a chemical reaction which sends nerve impulses to the brain. These impulses serve as messengers to tell the brain what the eyes are seeing. If vitamin A is abundant in the body, more visual purple is immediately formed. This continuous process involving the destruction and regeneration of visual purple lasts throughout life. Thus vitamin A aids in "photographing" what you see but the "film"—the visual purple—must be replaced each time after it has been "exposed." Failure to form more visual purple immediately leaves one unable to see in the dark.

No one knows the amount of vitamin A needed daily, and in fact, the requirement varies widely with individuals. The National Research Council recommends that adults receive 5,000 units of this vitamin every day, but this quantity is inadequate for persons whose occupation or recreation causes them to be exposed to bright light (which destroys vitamin A quickly) or to dim

light, which causes it to be used rapidly.

Partly because I use my eyes a great deal in writing, in addition to obtaining vitamin A from meals I take a capsule of natural fish-liver oil supplying 25,000 units of vitamin A with 2,500 units of vitamin D after both breakfast and dinner. I would recommend this quantity, or 50,000 units daily, for anyone exposed to an extremely bright or dim light, or who is already deficient in this vitamin.

Most adults, I believe, would profit by obtaining at least 25,000 units daily, especially if you drive a car at night. Vitamin A offers many advantages to health aside from good vision.

The vitamin A (carotene) from vegetable sources is not readily absorbed because it is held inside of cell walls. For example, one absorbs only about 1 per cent of the carotene available from raw carrots; 30 per cent from cooked carrots; and presumably 100 per cent from fresh carrot juice, though the vitamin is quickly destroyed by oxygen if the juice is allowed to stand. Furthermore, this vitamin is not absorbed unless taken with a meal supplying some fat.

Vitamin A is destroyed in the body by oxygen unless vitamin E is adequately supplied. Today, unfortunately, the average American receives far too little vitamin E, formerly supplied by unrefined and unhydrogenated vegetable oils, such as soybean, safflower, sunflower seed, peanut and wheat germ oils.

Generous amounts of vitamin A, absorbed by the aid of some fat and protected by an intake of 100 units or more of vitamin E daily, can help guard you against the highway hazard of night blindness. □

COMMON SOURCES OF VITAMIN A

This list is offered only as a general guide. Amounts of vitamin A vary widely with circumstances of growth, processing and preparation.

Food	Portion	A units
Cow's Milk, whole	1 qt.	3,000
Powdered Milk, whole	1 cup	1,100
Cream, heavy or whipping	½ cup	1,900
Eggs	2	1,200
Butter	¼ lb.	3,700
Margarine	¼ lb.	3,700
Liver, chicken, fried	3 med.	32,200
Liver, beef, sauteed	3½ oz.	53,400
Liver, calf	3½ oz.	32,000
Liver, lamb	3½ oz.	74,000
Liver, pork	3½ oz.	14,000
Beet Greens, steamed*	1 cup	5,100
Broccoli, steamed	1 cup	5,100
Carrots, cooked, diced	1 cup	18,130
Carrots, raw, grated	1 cup	13,000
Carrots, raw, strips	1 med.	5,000
Chard, steamed, leaves & stalks	1 cup	8,100
Collards, steamed, leaves	1 cup	11,700
Dandelion Greens, steamed	1 cup	27,300
Kale, steamed	1 cup	8,000
Mustard Greens, steamed	1 cup	10,050
Spinach, steamed	1 cup	11,800
Squash, winter, mashed	1 cup	6,100
Sweet Potatoes, baked	1 med.	11,600
Tomatoes, canned whole	1 cup	2,500
Tomatoes, raw	1 med.	2,600
Turnip Greens, steamed	1 cup	15,300
Apricots, canned in syrup	1 cup	4,500
Apricots, dried, uncooked	½ cup	8,000
Apricots, fresh	3 med.	2,900
Cantaloupe	½ med.	6,000
Cherries, canned, pitted (unsweetened)	1 cup	1,680
Orange Juice, frozen concentrate	6-oz. can	1,490
Papaya, fresh	½ med.	3,300
Peaches, canned, sliced	1 cup	1,100
Peaches, fresh, raw	1 med.	1,320
Prunes, cooked	1 cup	1,800
Pumpkin Pie	1 slice	2,460

*Vegetable sources supply carotene which is converted into Vitamin A in the body.

LETTERS TO AGENCY FROM VOL. 28 AND 35 OF
ADMINISTRATIVE RECORD

3220 Portage Bay Place East
Seattle, Washington 98102
February 10, 1973

Hearing Clerk
Room 6-88
Dept of HEW
5600 Fishers Lane
Rockville, Md. 20852

Dear Sirs:

I wish to protest your proposed maximum non-prescription potencies on vitamins A & D, as per your news release of December 13, 1972. I regularly take quantities of these vitamins in excess of your proposed limits, not as therapy for any disease under doctor's care, but merely as preventative measures to ensure adequate "fuel" to function in this stressful world. I do feel that this program I have established gives me greater vitality; I often modify the amount of food supplements I take according to how I feel. Surely no doctor's diagnosis is necessary for such simple preventative supplements to my diet; surely the excessive premium I would need pay the Druggist for his red tape would be superflous. Restrictions on these vitamins, or on any food supplements, are tantamount to restrictions on the types of food I may purchase through my grocer. For these reasons, I feel that the proposed potency restrictions are abridgements of my freedom of choice, and are thus not in the best interest of the citizens of America.

Sincerely,

Wayne D. Gilham

Wayne D. Gilham

Feb. 6, 1973

Hearing Clerk
Dept. of H.E.W.

Dear Sir;

In protest against the proposed amendment regarding vitamins A & D published in the Federal Register 12/14/72:

I demand the right to take vitamins A & D in excess of proposed limits without a doctors's prescription. Vitamins are food supplements, not drugs. There are many far more dangerous drugs on the market, but our right to purchase these has never been questioned. Let the burueacrats get off our backs, the American public can still think for themselves.

I demand a full hearing on this, and a hearing in Southern California.

My attorney in this matter is J. Joseph Matonis.

Yours, truly,

Lynn Standridge

Lynn Standridge

517 Fourth Avenue
Hinton, W.Va. 25951
February 9, 1973

Hearing Clerk, Dept. of H.E.W.
5600 Fishers Lane
Rockville, Maryland 20852

Gentleman:

I would like to go on record as bitterly opposing the FDA's proposal concerning restrictions of vitamins A and D to prescriptions only. This would impose extra expense on those purchasing the vitamins and would in many cases prohibit even buying them at all.

These vitamins are vital to us older citizens and to do without them or to have the dosage decreased would affect us both physically and psychologically. Such restrictions would be an infringement on our freedom as citizens of this great country of ours.

Nothing can possibly be gained in any area by such a move and it would certaintly limit the advantages.

Since I can do nothing else to help myself or others in this matter I am appealing to you to aid in stopping this proposal before it becomes a law of the land.

Respectfully Yours,

Mrs. J.O. Caldwell

Mrs. J.O. Caldwell

131 East Street
Colonia, New Jersey 07067
2-9-73

RE: Restrictions on Vitamins A and D

Dear Sir:

I hope the FDA will <u>not</u> be able to restrict amounts greater than 10,000 units of A and 400 units of D.

- Prescriptions cost the consumer excessively.
- The FDA did not mention the positive functions of these vitamins.
- The FDA did not mention:
  - the potencies taken
  - the period of time
  - the scientific authority for these claims.

Surely, if they must do something — why not label the vitamin bottles with a warning similar

to that on cigarette packaging. Surely, cigarettes:
1. have been proven dangerous to one's health
2. have no positive functions

and yet they are available to all freely.

I really feel that restricting my intake of Vitamins A & D is a violation and infringement of my constitutional rights. And putting more money into the "chemical-pharmaceutical complex" does not please me.

I sincerely hope reason & rationality survive & that the vitamins will not be restricted. I will be happy to testify my good health. I have been taking 25,000 units of A & 5,000 units of D daily for six years.

Respectfully,
Karen Kotros.

593a

1838 Ransom Road
Glendale, California
February 11, 1973

Department of Health, Education and Welfare
Hearing Clerk
5600 Fischers Lane, Room 6-88
Rockville, Md. 20852

Gentlemen:

Please add my name to those outraged citizens who are protesting banning the over the counter sale of Vitamins "A" and "D" and other food supplements which are being erronously labled "drugs".

Is this a political pay-off? Whose interests are being considered? Surely not those of the public.

Anyone knows vitamins are not medications. They are not drugs. They are food supplements and, as such, fulfill entirely different needs. What are the statistics of vitamin "A" or vitamin "D" toxicity as compared with the bad effects as a result of alcohol, tobacco or even candy? You mean to tell me that I can purchase a gallon of vodka or five pounds of candy or two cartons of cigarettes or a phony food item such as "Bacon Bits" or any number of foods with endless numbers of food "additives" and you will trust me not to over-indulge and, in my best interest, guarantee my well being? I can purchase Iodine by signing for it or any number of other poisons but NOT vitamins?

Absurd!

no wonder the U. S. bureaucracies have acquired a bad reputation. Are your brains in your feet? Why don't you direct your energies to a REAL problem? There surely are some thinking people around who could be added to your staff.

Tell me the name of a competent doctor who actually believes anyone is going to be better off with less vitamins than more?

Your endeavors to ban the sale of certain vitamins, except through prescriptions, are unbelievably retrogressive and cannot conceivably be considered in the best interest of the general public.

I am shocked that ANY U.S. governmental agency would be occupied with such primitive projects!

Very truly yours,

Mamie Boskovich
Mrs. Martin Boskovich

8660 ½ La Mesa Blvd.
La Mesa, Ca. 92041
February 9, 1973

Hearing Clerk
Dept. of Health, Education, + Welfare
5600 Fisher's Lane
Rockville, Maryland 20852

Dear Sir:

I object to the amendments to the Federal Drug Administration regulations published in the Dec. 14, 1972 Federal Register proposing to limit Vitamin A to 10,000 ~~mg~~ U.S.P. Units and Vitamin D to 400 ~~mg~~.

They are not a threat or danger. They are a food, not drugs and they should not be placed on a prescription status.

I demand a full public hearing and also a hearing in Southern California.

Sincerely yours,

(Mrs.) Osia Pawley

1435 – 30th St.
San Diego, Ca. 92102

2/8/73

Hearing Clerk – Dept. H. E. W.
Rockville, Md.

Dear sir or madam:

This is a request for a hearing in southern California, as well as in Washington, on the amendments to the regulations re. vitamins A + D (F. D. A.'s — published in the register Dec. 14, 1972.) Vitamins are not drugs! + People are not alike! – They need different amounts!

(Why don't they restrict sale of aspirin?!!) Please – let's have some common sense here!!?

Yours very truly,

Mary Hughes
(Mrs.)

1719 Laramie
Manhattan, Kansas 66502
February 7, 1973

Department of Health, Education and Welfare
Hearing Clerk
5600 Fishers Lane, Room 6-88
Rockville, Maryland 20852

Dear Sirs:

I am unable to see why some of the very items, namely Vitamin A and D, that are needed each day to support human life, seem to scare you to the point that they have to be obtainable by--"Doctors Prescription Only".

My education tells me that 25,000 I.U. of Vitamin A and 10,000 I.U. of Vitamin D can be taken continuously by adults without toxic affects. But for infants, as little as 1800 I.U. of Vitamin D can be toxic.

I would suggest that we stop making laws against the ingredients in our foods that cause our bodies to live. Instead, why not support life by allowing everyone the freedom to purchase those items they must have in order to live, in the quantities they really need?

The quantity of each individual food nutrient needed by each person is different, depending on the genetic code given him by his parents. One individual's genetic code may require him to need several times more of some food nutrient to keep his body healthy, than that of another individual's genetic code. When this individual is unable to obtain this food nutrient in the quantities his genetic code dictates, he has only one option left, and that is to get it from food, which is usually impossible with America's food distribution system.

While you're at it, let's make it a law that all salt used for human consumption be iodized.

Let's take the restrictions off the unusually small amount of iodine which is now allowed in vitamin and mineral supplements.

Let's allow Folic Acid to be sold in potencies that will build health, which is approximately 10 to 50 times the 0.1 mg. now allowed.

These are just a few of the many food nutrients that have been severely limited, which when all of them are taken in quantities needed as determined by each individual's genetic code, will work together to build a healthy mind and body.

I agree that it was necessary and needed, to have all food products show on the package their food content nutrient analysis.

Thank you for your time and consideration.

Sincerely yours,

Arris A. Sigle

Arris A. Sigle

cc: President Richard Nixon
Rich DeVos
W. Clement Stone

3932 Burke Ave. No.
Seattle, WA 98103
Feb. 6. 1973

Hearing Clerk
Dept. of Health, Education & Welfare
5600 Fishers Lane, Room 6-88
Rockville, Maryland 20852

Dear Sir:

Because our food is grown on increasingly poor soil, shipped greater distances, lays on the shelves longer with further loss of nutrients, it is almost impossible to get sufficient vitamins from a "normal" diet.

The taking of food supplements is almost imperative for health. The increased cost of getting vitamins by prescription would be prohibitive. Therefore, I am against the limitation of the potencies of vitamin A and D to 10,000 units and 400 units, respectively, by the FDA.

Yours very truly,

Cecile M. Cooper (Mrs. J. H.)

599a

1115 Wilson Rd
Wilmington, Delaware 198.
February 10, 1973

Department of Health, Education and Welfare
Hearing Clerk
5600 Fishers Lane,
Room 6-88
Rockville, Md. 20852

Gentlemen:

My freedom to decide for myself whether or not I want extra vitamins and minerials — more especially A+D as proposed by your office — is quite disturbing. If what you are proposing is done, it will vertually put small business out and permit drug stores and doctors to flourish more. It appears to me you are the pawns of AMA and large drug houses. What is your real reason to "KILL" the health foods industry? By the conservative figures of the USDA, 48% of American households suffer from one or more nutritional deficiencies

In regards to A+D — there is no statistics evidence of anyone dying from an "OVERDOSE" of vitamins — especially A+D; if toxicity does occur, it will be evidenced or noticed well in advance and when the dose is cut down or eliminated the symptoms and toxicity will disappear. It should also be brought to your attention that Vitamins are Not <u>DRUGS</u> but vitamins are

vital nutrients necessary for vital body functions and health. It appears that being pawns of the AMA and large drug-houses that this bureaucracy seems to be mesmerized into thinking that vitamins are drugs and are putting them in the same catagory as other DEATH PRODUCING DRUGS — such as aspirin. They do not advertise that you should take vitamins for a headache do they? As on other DRUGS they do not say "keep out of reach of children", do they?

I'm making a vehement protest and plea! PLEASE!! DO NOT infringe on my FREEDOM.

Yours truly,

S. Swinger

- pre-school
- kindergarten thru 6
- summer program
- adult seminars

601a

2/9/73

Dear friend,

I like to prevail upon you not to place vitamins A & D as " prescription item " .

The responsibility of taking the right amount rests with the people. After all, any food, taken in excess is detrimental to the human organism. The consumer needs to be protected from the unknown ingredients harmful to his health. His intelligence is to be trusted.

Thanking you for your help in this matter,

Cordially Yours,
Kenia Haidn

kenia haidn child house
20213 strathern street, canoga park, calif, 91306
341-4923

602a

Walter D. Rush
Plumsteadville, Pa. 18949
TEXACO SERVICE STATION
Fire Safety Equipment
Phone: 766-8131

Feb. 6 - 1973

Dept of Health,
Education + Welfare
Hearing Clerk - Dear sir -

Just recently I learned about the attempt of the F.D.A. to limit the ammount of Vitamin A (10,000 units) and Vitamin D (400 units) that may legally be used in any food supplement without prescripti
I believe this would be a step in the wrong direction.
I further believe that it is a selfish motive on the part of the F.D.A.
I am a firm believer in supplementing my diet with added vitamins, I am nearly 74 years old and I am in better health and enjoy life better than 35 or 40 years ago. In my younger years I did not understand the value of proper diet + nutrition.

In my opinion a physician, who has had his education and training in administering and prescribing drugs would hardly be the proper person to prescribe vitamins.

Ice-cream, for instance can also be injurious to the health if consumed in too large quantities, but I have never heard of legislating the use of ice-cream.

Yours in the interest of better health.

603a

P.O. Box 3[illegible],
Eureka, California 95501,
February 5th, 1973.

Department of Health, Education and Welfare,
5600 Fishers Lane, Room 6-88,
Rockville, Maryland, 20852.

Gentlemen: Attn: Hearing Clark

I am writing you at the direction of a very large group of citizens regarding the Federal Food and Drug Administration's proposed restrictions on Vitamins A and D.

The FDA has proposed that the maximum allowable potencies of Vitamin A and D in any food supplement be restricted to 10,000 units of Vitamin A and 400 units of Vitamin D. Potencies above these levels would be available by prescription only.

We, as a group, feel that we are entitled to take any potency of these two vitamins we desire. If toxic effects develop, all we have to do is cut down on the quantity and our toxic symptoms disappear. We have been taking a higher potency for many years and feel wonderful. If people are forced to buy through prescription, this costs them a lot more money and is another "boon" for the doctors and for the drug and chemical companies.

The Food and Drug Administration is supposed to protect public health, but in reality, their chief concern is in making it easy, by few restrictions, for the Chemical and Drug Companies to sell their products to the unsuspecting public.

We, as a group, have also been taking many different kinds of natural vitamins and minerals for years and feel much better in health for doing so. We all know that when we grow older, we need food supplements because our bodies cannot assimilate food as well as when we were younger. We also know that we don't get the needed vitamins and minerals in our food which is supposedly "enriched" with all kinds of chemicals.

By the conservative figures of the Department of Agriculture, 48% of American households suffer from one or more nutritional deficiencies. Of those whose nutrition can be considered good, a large proportion use vitamin and mineral supplements regularly. These indisputable facts PROVE that FDA is doing a rotten job.

We earnestly urge you to help us any way you can to keep our higher potencies of natural Vitamins A and D.

Sincerely,

(Mrs.) May L. Freeman

55 Magnolia Ave., Apt. #1
San Anselmo, Calif. 94960
February 3, 1973

Department of Health, Education & Welfare
5600 Fishers Lane, Room 6-88
Rockville, Maryland 20852

Attn: Hearing Clerk

Dear Sir:

I wish to protest intended action to restrict potencies on Vitamins A and D.

Do you also intend to require a prescription to buy carrots (18,300 units per cup), dandelion greens (27,300 units per cup), beef liver (53, 400 units for 3½ oz), and chicken livers (32,200 units for 3 medium size)? Many people either prefer or find it necessary to take vitamins instead of the above foods. Certainly as "free Americans" we should have the right to choose what and how much of any food we wish to consume without obtaining a prescription. And it must be admitted that vitamins are a food and not a drug.

This restriction appears to be another example of forcing prices higher in an area where they are already too high. I urge you not to let this happen. Let's keep the drug business out of the food business.

Sincerely yours,

Rita M James

Rita M. James

605a

February 3, 1973

Department of Health, Education & Welfare
Hearing Clerk
5600 Fishers Lane, Room 6-88
Rockville, MD. 20852

To whom it may concern:

I have recently heard about the proposed limitation on the dosage of vitamin A.

I understand the concern of the Department in this matter. It is true that too much vitamin A can be harmful. These harmful effects can, however, be removed by simply cutting down on the vitamin A intake. I feel very strongly that what is needed is more knowledge, not more restrictions.

There is a growing segment of the U.S. population which is increasingly knowledgeable about nutrition and which is finding great benefits in health through self-prescribed "vitamin therapy" and practices of good nutrition. It is an imperfect method to be sure, and there are some dangers, but it can also be very vitally beneficial.

It would certainly be preferable to have an expert tell one what to eat and what vitamins to take. However, finding a doctor who is also a nutritionist or even very knowledgeable about nutrition is like finding the proverbial needle-in-a-haystack.

I think I am fairly representative of the group of people who are trying to improve their health through improved nutrition. Unfortunately, with our soils depleted by chemical fertilizers and our foods sprayed with poisons, treated, refined, etc., it is not always possible to fulfill one's vitamin requirements through diet alone. So, like many others, I take vitamin supplements. Also, each individual has individual nutritional requirements. Through reading and experimentation I have come to know what my daily requirements are and my health has improved markedly since I have begun to follow these self-established guidelines.

I would prefer to go to someone more knowledgeable than I but unfortunately I have not been able to find anyone (doctor or otherwise) to go to! Hopefully physicians will become more sophisticated in this area as more people become interested, but for now there are many like myself who are self-treated and very successfully so. In my case, I have found that my daily requirements for some vitamins is more than what is listed in the tables. I have established my dosages by a very simple method: I discovered the minimum below which there were ill effects (In the case of vitamin A the ill effects are seen in my complexion. I have tried many times to lower the dosage (being aware of possible ill effects and wanting to avoid taking too much) and always with the same result -- skin problems. I have been taking over 50,000 units a day for two years WITH NO ILL EFFECTS.).

It would be a great hardship for people like me to have to pay the exorbitant costs of prescription drugs just to get our daily requirements of vitamins! plus the cost of seeing a doctor to get the prescription in the first place.

Rather than penalizing those who are successfully improving their health through their own knowledge and practice of good nutrition, I suggest you take the following action:

Require a statement on the label of all vitamins of

(1) the recommended daily minimum requirement, and
(2) the symptoms of overdose and the antidote.

There is so much that needs to be done by the Food & Drug Administration: requiring more truth in labelling, banning some of the harmful additives and preservatives in our foods, setting limits on profits made by prescription drug companies (or if there are limits, lowering them -- drug costs are prohibitive!); in general letting people know what is really in the product they are buying and how it was prepared, and watching over the honesty of the producers or manufacturers. Let's have more information and knowledge about these matters, not a step backward to remove something as potentially beneficial as vitamins from the hands of those who perhaps cannot afford "prescription vitamins"!

Sincerely,

Phyllis Mottola

Phyllis Mottola

c/o WICHE
P. O. Drawer P
Boulder, CO. 80302

607a

2912 Fulton Street, #D
Berkeley, California 94705

February 5, 1973

Department of Health, Education & Welfare
Hearing Clerk
5600 Fishers Lane, Roo[illegible] 88
Rockville, Maryland 20852

Dear Sirs;

I am most indignant at your recently published order of January 19 limiting the future capsular availability of vitamin and mineral supplements. I do not believe you have any scientific evidence to support this supposedly necessary limitation. Vitamins A and D are the ONLY vitamins that have any apparent toxidity and this disappears when the dosage is reduced. Granted that you might feel this reason enough to limit those two vitamins, it is still no reason to limit the available dosages in all the other vitamins. At this time, when we are just beginning to understand and recognize the enormously beneficial effects of vitamins C and E (to mention just two), it seems increased research would be in order. What you are attempting to do is none other than criminal. The Food and Drug Administration should be an agent of all the people of the United States and act to further their interests, NOT the interests of the Pharmaceutical and American Medical Associations. As there is no danger of my taking large doses of vitamins and minerals (or if there is, I prefer to take the risk), it is my civil right to be able to do so. No agent of the government should be able to limit my freedom in the personal matter of the health of MY body.

I urge you to reconsider this matter and to alter your January 19 order. The time and energy should rather be spent on the real drug problems existant in the country, and increased research should be done into the benefits to be derived from vitamin/mineral supplements. Too little is known in the area of Nutrician. Medical students should study nutrician extensively in medical school. If we are to have a medical practice that is truly preventive and not just cure-oriented, subjects like the use of supplements should be thoroughly studied as part of the medical school curriculum. Since the situation at present is that practicing doctors know no more about nutrician than myself, my husband or neighbor (they may, indeed, know considerably less), it is therefore rather careless to say that they should be responsible for prescribing any vitamin/mineral supplements beyond the minimum daily allowance. You are attempting to create a bureaucratic structure where there was none before by involving a doctor and a drugist who are entirely unnecessary. Further, since the MDR dosages are merely the amounts necessary to prevent disease (e.g., scurvey), you are not acting to promote the health of the American people, which should be your primary concern. What valid reason could you possibly have for this order?

I await your action and response.

Sincerely,

Carolyn Smith

(Mrs.) Carolyn Smith

cc: Congressman Dellums
Senator Cranston
Senator Tunney

608a

467 [illegible]kshire Road
Severna Park, Maryland, 21146

Department of Health, Education & Welfare
5600 Fishers Lane
Room 6 -88
Rockville, Maryland, 20852
Attention: Hearing Officer
Dear Sir;

This is my protest against any bill that would limit and regulate the sale of Vitamins A & D.

Actually, I feel that this issue is a complete fraud on the people and just a foot in the door toward regulating all vitamin supplements. We as a people are already being weakened by the drugs which are allowed to be fed to the livestock from which we derive our table meats, the packages and cans on the grocer's shelves which have had the nutrients removed and chemicals added. Vitamin supplements are really our only way to good health.

Are we, who are concerned enough to read and study about the nutrition that is needed by our bodies, to be deprived of our sovereign right to use these products as we see fit. A person may obtain one and one-half the so called minimum daily requirement of vitamin A by drinking a glass of carrot juice, will that be also limited? Cigarettes were not banned, or cut in half, or the amount regulated, they were just labeled so that people could use their own discretion. We may purchase all of the alcoholic beverages that we desire, and nothing could be worse for the health.

A nation can only be as strong as its individual citizens are healthy. Please do not deprive us of the right to think, and of the nutrients which enable us to do so.

Sincerely yours,

Emily D. Sachs

609a 368 Vista St #97
Chula Vista, Cal
Feb 6, 1973

Hearing Clerk
Dept of H E W
Rockville, Maryland

Sirs!

I object to the proposed regulations published in the December 14, 1972 Federal Register.

I demand the right to be able to take Vitamins A and D in excess of the proposed limits without a Dr. prescription. Vitamins are food and not drugs. Many dangerous drugs are available without prescription such as aspirin, excedrin, buffirin, Sleep Ease, No Doze, etc. some of them "uppers" and "downers" which kills users to drug themselves.

Death foolers are not "bizarre". Dr. Chas. Edwards M.D. is bizarre in his ideas.

I demand a full hearing.

Sincerely
E. K. and Lee Bernikin.

610a

560 Lincoln Ave.
Pomona, Calif.
9 February 1973

Hearing Clerk
Department of Health, Education, and Welfare

Dear sir:

This letter is in reference to the proposed reduction in potency of non-perscription vitamins A and D. This is an infringement of our freedom. Toxicity from vitamins A and D occurs rarely and only from long term usuage of excessively high dosages; on the other hand, many people, ourselves included, have derived great benefits from taking these vitamins in larger dosages than the recommended daily allowance. There are research projects which indicate that healthy people can derive improved health from larger daily intakes of these vitamins than the RDA. In contrast, non-perscritpion drugs which offer nothing but symptomatic relief will continue to be available; some of these, aspirin as a prime example, often produce toxic effects in the recommended dosages from even short term usuage. We repeat, removing the currently available potencies of vitamins A and D from the market is a violation of our freedom of choice. We demand that this proposal not be implemented.

Michael Akey
Marie Akey
Bessie Sullivan

611a

Miss T. K. Travis
219 E. Park St., #1
Stockton, CA 95202

February 6, 1973

Hearing Clerk
Department of Health, Education
and Welfare
5600 Fishers Lane, Room 6-88
Rockville, MD 20852

Dear Sir:

A few weeks ago, I received the news that your Department proposes to limit the dosage of Vitamins A and D "to safeguard the public from the potentially toxic effects from consumption of high potencies of these two vitamins over an extended period of time." At face value, this appears to be an earnest attempt to save the public from themselves; however, there are several arguments I have against this proposal, which I humbly submit for your perusal.

There are many people who depend on higher potencies of Vitamins A and D in their systems than others, just as there are some who depend more than others on what would appear to be massive quantities of food, just to stay healthy and/or alive. If we must rely on prescriptions to fulfill our vital needs from sources equivalent to food, we would be penalized for our attempts to live by costs we are unable to meet in proportion to our net income.

Another consideration is the psychological effect your proposal might have on the people you allegedly want to "safeguard." You are saying, in effect, that people do not have enough sense to know what is good for them. You are implying that we are incapable of reading the ample literature available to the public, and the vitamin bottle lables, that clearly give recommendations of daily dosage, their uses and the effects of their abuse.

A third hole I see in your proposal is the ambiguity of your statement that "high potencies of these two vitamins over an extended period of time" is "toxic." I would appreciate any specific explanation of what you mean by this. Through personal experience, I have found that vitamins are not as alcohol or tobacco in being lastingly toxic, yet I have heard of no measures to limit to medical prescription either of these two dangerous drugs freely open to adults. Vitamins are as food, in nourishment and the elastic way "toxic effects" leave, the moment a given person ceases to overdose--or overeat.

Even if the proposed measure were passed, those who really want more would obtain it through their own methods, legal or otherwise.

The same fatalities you profess to want to stifle would exist. The only perceivable change would be more expense and less availability of vitamins to the public.

I trust you will compare the weight of value of your proposal to my arguments against it and judge accordingly. I trust other concerned people as myself will have some effect on your final decision.

Thank you.

T. K. Travis

94TH CONGRESS 2d Session } HOUSE OF REPRESENTATIVES { REPORT No. 94-1005

HEALTH RESEARCH AND HEALTH SERVICES AMENDMENTS OF 1976

APRIL 2, 1976.—Ordered to be printed

Mr. STAGGERS, from the committee of conference, submitted the following

CONFERENCE REPORT

[To accompany H.R. 7988]

The committee of conference on the disagreeing votes of the two Houses on the amendment of the Senate to the bill (H.R. 7988) to amend the Public Health Service Act to revise and extend the program under the National Heart and Lung Institute, to revise and extend the program of National Research Service Awards, and to establish a national program with respect to genetic diseases; and to require a study and report on the release of research information, having met, after full and free conference, have agreed to recommend and do recommend to their respective Houses as follows:

That the House recede from its disagreement to the amendment of the Senate and agree to the same with an amendment as follows:

In lieu of the matter proposed to be inserted by the Senate amendment insert the following:

SECTION 1. (a) This Act may be cited as the "Health Research and Health Services Amendments of 1976".

(b) Whenever in this Act (other than in titles III, V, VI, VII, and XI) an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be made to a section or other provision of the Public Health Service Act.

TITLE I—REVISION OF NATIONAL HEART AND LUNG INSTITUTE PROGRAMS

SEC. 101. (a) Congress finds and declares that—

(1) diseases of the heart, blood, and blood vessels collectively cause more than half of all the deaths each year in the United States and the combined effect of the disabilities and deaths from such diseases is having a major social and economic impact on the Nation;

57-006 O—76——1

greatest number of persons who will benefit from and are in need of the services provided under such programs.

"(c) In making grants and entering into contracts for any fiscal year under section 301 for projects described in section 1102 or under section 1101 the Secretary shall give special consideration to applications from entities that received grants from, or entered into contracts with, the Secretary for the preceding fiscal year for the conduct of comprehensive sickle cell centers or sickle cell screening and education clinics.

"PUBLIC HEALTH SERVICE FACILITIES

"SEC. 1105. The Secretary shall establish a program within the Service to provide voluntary testing, diagnosis, counseling, and treatment of individuals respecting genetic diseases. Services under such program shall be made available through facilities of the Service to persons requesting such services, and the program shall provide appropriate publicity of the availability and voluntary nature of such services.

"REPORTS

"SEC. 1106. (a) The Secretary shall prepare and submit to the President for transmittal to the Congress on or before April 1 of each year a comprehensive report on the administration of this part.

"(b) The report required by this section shall contain such recommendations for additional legislation as the Secretary deems necessary.".

(b)(1) Section 1121(b)(5) is amended by striking out "ending June 30," each place it occurs.

(2) Parts C and D are redesignated as parts B and C, respectively.

(3) The heading of such title is amended to read as follows:

"TITLE XI—GENETIC DISEASES, HEMOPHILIA PROGRAMS, AND SUDDEN INFANT DEATH SYNDROME."

(c) The amendments made by subsections (a) and (b) shall take effect July 1, 1976.

TITLE V—FEDERAL FOOD, DRUG, AND COSMETIC ACT AMENDMENTS

SEC. 501 (a) Chapter IV of the Federal Food, Drug, and Cosmetic Act is amended by adding after section 410 (21 U.S.C. 349) the following new section:

"VITAMINS AND MINERALS

"SEC. 411. (a)(1) Except as provided in paragraph (2)—

"(A) the Secretary may not establish, under section 201(n), 401, or 403, maximum limits on the potency of any synthetic or natural vitamin or mineral within a food to which this section applies;

"(B) the Secretary may not classify any natural or synthetic vitamin or mineral (or combination thereof) as a drug solely because it exceeds the level of potency which the Secretary determines is nutritionally rational or useful;

"(C) the Secretary ma
403, the combination or n
"(i) vitamin,
"(ii) mineral, or
"(iii) other ingred
within a food to which thi

"(2) Paragraph (1) shall n
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of twelve years.

"(b)(1) A food to which this
section 403 to be misbranded u
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"(2)(A) The labeling for any
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use for which a food purports or
not limited to the following:

"(A) Supplying a specia
a physical, physiological, pa
but not limited to the conditi
lactation, infancy, allergic
overweight, or the need to con

"(C) the Secretary may not limit, under section 201(n), 401, or 403, the combination or number of any synthetic or natural—

"(i) vitamin,

"(ii) mineral, or

"(iii) other ingredient of food,

within a food to which this section applies.

"(2) Paragraph (1) shall not apply in the case of a vitamin, mineral, other ingredient of food, or food, which is represented for use by individuals in the treatment or management of specific diseases or disorders, by children, or by pregnant or lactating women. For purposes of this subparagraph, the term 'children' means individuals who are under the age of twelve years.

"(b)(1) A food to which this section applies shall not be deemed under section 403 to be misbranded solely because its label bears, in accordance with section 403(i)(2), all the ingredients in the food or its advertising contains references to ingredients in the food which are not vitamins or minerals.

"(2)(A) The labeling for any food to which this section applies may not list its ingredients which are not vitamins or minerals (i) except as a part of a list of all the ingredients of such food, and (ii) unless such ingredients are listed in accordance with applicable regulations under section 403. To the extent that compliance with clause (i) of this subparagraph is impracticable or results in deception or unfair competition, exemptions shall be established by regulations promulgated by the Secretary.

"(B) Notwithstanding the provisions of subparagraph (A), the labeling and advertising for any food to which this section applies may not give prominence to or emphasize ingredients which are not—

"(i) vitamins,

"(ii) minerals, or

"(iii) represented as a source of vitamins or minerals.

"(c)(1) For purposes of this section, the term 'food to which this section applies' means a food for humans which is a food for special dietary use—

"(A) which is or contains any natural or synthetic vitamin or mineral, and

"(B) which—

"(i) is intended for ingestion in tablet, capsule, or liquid form, or

"(ii) if not intended for ingestion in such a form, does not simulate and is not represented as conventional food and is not represented for use as a sole item of a meal or of the diet.

"(2) For purposes of paragraph (1)(B)(i), a food shall be considered as intended for ingestion in liquid form only if it is formulated in a fluid carrier and it is intended for ingestion in daily quantities measured in drops or similar small units of measure.

"(3) For purposes of paragraph (1) and of section 403 (j) insofar as that section is applicable to food to which this section applies, the term 'special dietary use' as applied to food used by man means a particular use for which a food purports or is represented to be used, including but not limited to the following:

"(A) Supplying a special dietary need that exists by reason of a physical, physiological, pathological, or other condition, including but not limited to the condition of disease, convalescence, pregnancy, lactation, infancy, allergic hypersensitivity to food, underweight, overweight, or the need to control the intake of sodium.

"(B) Supplying a vitamin, mineral, or other ingredient for use by man to supplement his diet by increasing the total dietary intake.

"(C) Supplying a special dietary need by reason of being a food for use as the sole item of the diet.".

(b) The Secretary of Health, Education, and Welfare shall amend any regulation promulgated under the Federal Food, Drug, and Cosmetic Act which is inconsistent with section 411 of such Act (as added by subsection (a)) and such amendments shall be promulgated in accordance with section 553 of title 5, United States Code.

SEC. 502. (a)(1) Section 403(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(a)) is amended (A) by inserting "(1)" after "If", and (B) by inserting before the period at the end a comma and the following: "or (2) in the case of a food to which section 411 applies, its advertising is false or misleading in a material respect or its labeling is in violation of section 411(b)(2)".

(2)(A) Section 201(n) of such Act is amended by inserting "or advertising" after "labeling" each time it occurs.

(B) Section 303 of such Act is amended by adding at the end the following new subsection:

"(d) No person shall be subject to the penalties of subsection (a) of this section for a violation of section 301 involving misbranded food if the violation exists solely because the food is misbranded under section 403(a)(2) because of its advertising, and no person shall be subject to the penalties of subsection (b) of this section for such a violation unless the violation is committed with the intent to defraud or mislead.".

(C) Section 304(a) of such Act (21 U.S.C. 334(a)) is amended by adding after paragraph (2) the following new paragraph:

"(3)(A) Except as provided in subparagraph (B), no libel for condemnation may be instituted under paragraph (1) or (2) against any food which—

"(i) is misbranded under section 403(a)(2) because of its advertising, and

"(ii) is being held for sale to the ultimate consumer in an establishment other than an establishment owned or operated by a manufacturer, packer, or distributor of the food.

"(B) A libel for condemnation may be instituted under paragraph (1) or (2) against a food described in subparagraph (A) if—

"(i)(I) the food's advertising which resulted in the food being misbranded under section 403(a)(2) was disseminated in the establishment in which the food is being held for sale to the ultimate consumer,

"(II) such advertising was disseminated by, or under the direction of, the owner or operator of such establishment, or

"(III) all or part of the cost of such advertising was paid by such owner or operator; and

"(ii) the owner or operator of such establishment used such advertising in the establishment to promote the sale of the food.".

(b) Chapter VII of such Act is amended by adding after section 706 (21 U.S.C. 376) the following new section:

"ADVERTISING OF CERTAIN FOODS

"SEC. 707. (a)(1) Except as provided in subsection (c), before the Secretary may initiate any action under chapter III—

"(A) with respect to any food which the Secretary determines is misbranded under section 403(a)(2) because of its advertising, or

"(B) with respect to
determines causes the foo
the Secretary shall, in accord
the Federal Trade Commissi
take respecting such food or a

"(2) The notice required b

"(A) contain (i) a de
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to be misbranded, and

"(B) be accompanied
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"(b)(1) If the Secretary n
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respect to a food or food ac
Secretary in writing, within
the receipt of such notice, tha

"(A) it has initiated u
investigation of such ad
such Act or any order or

"(B) it has commenc
under section 5, 13, or
Attorney General has co
action under section 5 w

"(C) it has issued an
complaint under section
or

"(D) pursuant to secti
tion to the Attorney Gen
the Secretary may not, except
action described in the Secreta

"(2) If, before the expira
date the Secretary receives a
Federal Trade Commission i
subsection (a)—

"(A) the Commission
a civil action described
this subsection respectin
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dvertising, or

"(C) the Commission
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the Attorney General, b
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the Secretary may, after the
described in the notice to the
Commission shall promptly

JOINT EXPLANATORY STATEMENT OF THE COMMITTEE OF CONFERENCE

The managers on the part of the House and the Senate at the conference on the disagreeing votes of the two Houses on the amendment of the Senate to the bill (H.R. 7988) to amend the Public Health Service Act to revise and extend the program under the National Heart and Lung Institute, to revise and extend the program of National Research Service Awards, and to establish a national program with respect to genetic diseases; and to require a study on the release of research information, submit the following joint statement to the House and the Senate in explanation of the effect of the action agreed upon by the managers and recommended in the accompanying conference report:

The Senate amendment struck out all of the House bill after the enacting clause and inserted a substitute text.

The House recedes from its disagreement to the amendment of the Senate with an amendment which is a substitute for the House bill and the Senate amendment. The differences between the House bill, the Senate amendment, and the substitute agreed to in conference are noted below, except for clerical corrections, conforming changes made necessary by agreements reached by the conferees, and minor drafting and clarifying changes.

TITLE I—REVISION OF NATIONAL HEART AND LUNG INSTITUTE PROGRAMS

Findings

The Senate amendment, in a provision not in the House bill, specified Congressional findings, with respect to the impact of diseases of the heart, lung and blood vessels and blood disease and the need for the proposed legislation.

The conference substitute conforms to the Senate amendment, with technical changes.

Advisory Council

The House bill changed the name of the National Heart Lung Advisory Council to the National Heart, Lung and Blood Advisory Council.

The Senate amendment contained no comparable provision.

The conference substitute conforms to the House bill.

Experts and Consultants

Existing law authorizes the Director of the National Heart and Lung Institute to obtain the services of not more than 50 experts and consultants.

marked 10 percent of the sums appropriated each year under the authority for research projects with respect to Cooley's anemia. The Senate amendment further provided for a separate authorization for sickle cell anemia research of $15 million for each of fiscal years 1976, 1977, and 1978.

The conference substitute conforms to the House bill, except that the Secretary is directed, in making grants and entering into contracts for research projects, to give priority to applications which are submitted for research on sickle cell anemia or for research on Cooley's anemia.

Title V.—Vitamins and Minerals

The Senate amendment contained provisions not included in the House bill relating to regulation of vitamin and mineral products under the Federal Food, Drug, and Cosmetic Act (hereinafter referred to as "the Act").

Under the Senate amendment, the Secretary of Health, Education and Welfare would generally have been prohibited from establishing maximum limits on the potency of vitamins or minerals in dietary supplements or classifying vitamins or minerals as drugs solely because they exceeded the level of potency determined by him to be nutritionally rational or useful. In addition, the Secretary would have been prohibited from limiting the combination of vitamins, minerals or other ingredients in dietary supplements. However, under the Senate amendment, the Secretary would have retained full authority to limit the potencies and combinations of vitamins, minerals and other ingredients in foods in the exercise of his authority under chapter V of the Act (relating to drugs) and under provisions of the Act respecting unsafe foods which are not generally recognized as safe. In addition, the Senate amendment contained provisions rendering the amendment's limitations on the authority of the Secretary inapplicable to vitamin and mineral products for use by children or by pregnant or lactating women.

The Senate amendment also contained provisions with respect to the labeling and advertising of vitamin and mineral products. It prohibited a product containing vitamins or minerals from being deemed misbranded solely because its label lists all ingredients of such a product. However, the amendment required that the labeling of such products could not list ingredients which are not vitamins or minerals except as a part of a list of all ingredients of the product and unless such ingredients are listed in accordance with applicable regulations. Moreover, the Senate amendment prohibited the labeling of or advertising for any such product to give prominence to or emphasize ingredients which are not vitamins or minerals or are not represented as a source of vitamins or minerals.

In addition, the Senate amendment afforded the Secretary significant new authority with respect to the advertising of certain products containing vitamins or minerals. (Under existing law, the Federal Trade Commission has exclusive authority with respect to the advertising of such products.) Under the Senate amendment, such products would be deemed misbranded if their advertising were false or misleading in a material respect. However, criminal penalties could not be imposed against persons who were in violation of the prohibitions against false or misleading advertising unless such a violation

was committed with the intent to defraud or mislead. Further, such products which are misbranded because their advertising is false or misleading in a material respect and are held for sale to the ultimate consumer in an establishment not owned by a manufacturer, packer or distributor, could not be seized unless (1) the advertising was disseminated in the establishment in which the product was held for sale to the ultimate consumer, the advertising was disseminated by or under the direction of the owner or operator of such establishment, or all or part of the cost of such advertising was paid for by the owner or operator, and (2) the owner or operator used the advertising to promote the sale of the product. Finally, the Senate amendment required the Secretary to consult with the Federal Trade Commission prior to initiating action with respect to such products deemed misbranded because of their advertising.

The Conference substitute conforms to the Senate amendment except that:

(1) It adds two technical amendments (clarifying the intention of the Senate amendment) to provide specifically that foods represented for use by individuals in the treatment or management of specific diseases or disorders and foods represented for use as the sole item of a meal or of the diet are excluded from the limitations on the Secretary's authority.

(2) Except in instances in which immediate action is necessary to eliminate an imminent hazard to health, it requires the Secretary to provide notification to the Federal Trade Commission of his intention to initiate an action with respect to false or misleading advertising, and it affords the Federal Trade Commission the opportunity to take specific enforcement action against false or misleading advertising for a period of up to 90 days before the Secretary may take comparable action.

Since the House has taken no action during this Congress with respect to this matter, it is important to provide more legislative history concerning these complex new provisions. Thus, presented below is a detailed description of the new provisions, as well as statements of the intentions of the managers with respect to their implementation.

Products Subject to the Conference Substitute

Under the conference substitute, products subject to its provisions are defined as safe human foods for special dietary use which are or contain any natural or snythetic vitamin or mineral and which are intended for ingestion in tablet or capsule form or in small units of liquid measure. In addition, such foods not intended for ingestion in tablet, capsule, or liquid form are subject to the provisions of the substitute only if they do not simulate conventional foods, if they are not represented to be conventional foods, and if they are not represented for use as the sole item of a meal or of the diet.

The definition of "special dietary use" in the conference substitute applies only to the foods to which the substitute is applicable and not to other foods, such as foods represented for use by infants or foods represented for use as the sole item of a meal or of the diet, that may be subject to 403(j) of the Act.

Thus, vitamins and minerals in tablet, capsule, or liquid form as well as those products which are represented for special dietary use in humans and which do not simulate and are not represented as conventional foods or substitutes for conventional foods and which are not represented for use as the sole item of a meal or of the diet, are products subject to the provisions of the substitutes.

Except with respect to products defined above, the conference substitute does not alter existing provisions of the Federal Food, Drug, and Cosmetic Act with respect to foods and drugs.

The Secretary retains his current authority to regulate the nutritional formulation and composition of, and potency of vitamins, minerals and other ingredients in conventional foods such as milk, enriched bread and enriched rice, as well as in products which simulate conventional foods such as soybased protein substitutes for meats and poultry. The Secretary also retains his current authority to regulate the nutritional formulation and composition of, and potency of vitamins, minerals and other ingredients in foods represented by labeling, advertising, or other promotional materials for use as the sole item of a meal or of the diet. Because consumers purchase these foods as nutritional equivalents of a well-balanced meal or diet, the conferees believe it is essential that the consumer of such products can be confident that a meal or diet based upon such products is nutritionally adequate and balanced and provides for the proper maintenance of the user's health for the duration of his use of these products.

Limitations on the Secretary's Authority

Under the conference report, three significant restrictions would be imposed on the Secretary with regard to the regulation of products subject to the conference substitute. First, new section 411(a)(1)(A) of the Act prohibits the Secretary from using his existing authority under sections 201(n) or 403 of the Act (relating to misbranding) or under section 401 of the Act (relating to standards of identity) to impose maximum limits on the potency of safe vitamins and minerals contained in products subject to the conference substitute. This provision would not restrict the Secretary from prescribing minimum potency levels for vitamins or minerals in such products in order to prevent the addition of insignificant or useless amounts.

Second, new section 411(a)(1)(B) of the Act prohibits the Secretary from classifying as a drug a natural or synthetic vitamin or mineral, offered by itself or in combination, solely because it exceeds the level of potency that the Secretary determines is nutritionally rational or useful.

Third, new section 411(a)(1)(C) of the Act prohibits the Secretary from using his authority with respect to misbranding or establishment of standards of identity to limit the combination or number of any safe vitamin, mineral or other ingredient of food in products subject to the conference substitute.

Exceptions to Limitations on the Secretary

Under the conference substitute (proposed new section 411(a)(2) of the Act), the limitations on the Secretary, described above, do not apply with respect to a product otherwise subject to the provisions

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(1973); *Abbott Labora*

of the conference substitute where such product is represented for use by (1) individuals in the treatment or management of specific diseases or disorders, (2) children, or (3) pregnant or lactating women.

The provision with respect to foods intended for use in the treatment or management of specific diseases or disorders was adopted in conference in order to make clear that the proposed new section 411(a) of the Act does not override the Secretary's authority under sections 401, 403, or 201(n) of the Act to limit the potency and combination of vitamins, minerals, other ingredients in foods, or foods, represented for use in the dietary treatment or management of individuals with specific diseases or disorders, or of post-operative or convalescing medical patients. Since each of these foods must be precisely formulated to meet the needs of individuals with specific diseases and disorders, the conferees believe it to be important that the language in the conference substitute clearly preserve the authority of the Secretary to regulate as foods the nutritional formulation, composition, and potency of each product represented for such uses. Inclusion of this language is not, however, intended to permit the Secretary to limit (under sections 401, 403, or 201(n) of the Act) the potency or combination of a safe vitamin, mineral, food ingredient, or food represented in its labeling and advertising to be solely for use by adults, other than pregnant or lactating women, as a nutritional supplement to general human dietary intake.

Dietary management with these products is not only of major clinical value to the individual, but can be lifesaving in many instances. In the case of a number of inborn abnormalities of metabolism, such as phenylketonuria and maple syrup urine disease, these foods provide the only means for prevention of mental retardation, particularly in infants and young children, or for the partial restoration of mental capacity in older children. Special formula feedings are essential to long-term maintenance of severely debilitated individuals. Low sodium foods are useful in dietary management of individuals with severe forms of hypertension, acute heart failure, acute nephritis, toxemias of pregnancy and similar disorders when the degree of sodium restriction must be greater than that achievable with conventional foods. Chemically defined formula diets are extremely useful for nutritional management of patients prior to and subsequent to gastrointestinal surgery.

The Senate amendment included, in proposed new section 411(a)(2) of the Act, a specific reference to the Secretary's authority to act by regulation. This reference was deleted by the conferees as unnecessary. It is not intended that the omission of this reference should be understood as in any way restricting the Food and Drug Administration's present authority to adopt regulations defining and enforcing the provisions of the Act. The Secretary in recent years has relied increasingly on administrative rulemaking to enforce the requirements of the law. Rulemaking affords opportunity for broader participation in the formulation of agency policy, promotes clarity of legal requirements, and assures equitable application of the law, while at the same time it reduces the cost to the taxpayer of case-by-case enforcement. The Secretary's legal authority, under section 701(a) of the Act, to adopt binding regulations has been recognized by the Supreme Court. *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973); *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967). This

authority has recently been upheld by the United States Court of Appeals for the Second Circuit. *National Nutritional Foods Assn. v. Weinberger*, 512 F. 2d 688 (C.A. 2, 1975).

For the purposes of the conference substitute, the term "children" is defined to mean individuals under the age of 12 years. The conferees are also concerned that attention should be given to those vitamin and mineral preparations that are not intended for use by infants children or pregnant or lactating women, but may be taken by or administered to them inadvertently. Just as the fetus may be affected by excessive doses of some food supplements, excessive doses of vitamins and minerals taken by children during the period of rapid growth and maturation can interfere with their normal development. Because of such possibilities of unrecognized or unanticipated harm, it is intended that the Secretary retain full authority to promulgate regulations designed to assure that unsuitable or inappropriate vitamin and mineral preparations are not inadvertently administered to individuals in these vulnerable groups.

Except as specifically provided, the conference substitute does not alter the drug or food provisions of the Federal Food, Drug, and Cosmetic Act. If a product containing vitamins, minerals or other ingredients is a drug within the meaning of section 201 (g) of the Act, the Secretary may, with respect to such product, exercise his authority under Chapter V of the Act. For example, the Secretary may bring an action for misbranding of a product which purports to be or is represented as a drug (within the meaning of section 201 (g) of the Act) if its labeling fails to bear adequate directions for its purported use or for the use for which it is represented (within the meaning of section 502 (f)(1) of the Act). See *V. E. Irons, Inc. v. United States*, 244 F. 2d 34 (C.A. 1, 1957); *Alberty Food Products v. United States*, 194 F. 2d 463 (C.A. 9, 1952); *United States v. Vitasafe Co.*, 345 F. 2d 864 (C.A. 3, 1965); *United States v. Article of Drug . . . B-Complex Cholinos Capsules*, 362 F. 2d 923 (C.A. 3, 1966).

The Secretary also has the authority to regulate the composition and potency of a product subject to the provisions of the conference substitute on the basis of safety. If a high potency preparation of a vitamin or mineral is a drug as defined by section 201 (g) of the Act and the Secretary determines that within the meaning of section 503 (b) of the Act, it is not safe for use except under the supervision of a physician, such a high potency preparation is subject to regulation as a prescription drug under the Act.

Similarly, if any vitamin, mineral or other food ingredient is not generally recognized as safe by qualified experts and meets the other criteria of the definition of a "food additive" under section 201 (s) of the Act, it would be subject to regulation under section 409 of the Act. If such a vitamin, mineral or other ingredient is intentionally added to a food, such food is adulterated (within the meaning of section 402 (a)(2)(C) of the Act) unless its use is in conformity with a regulation issued by the Secretary which prescribes the conditions under which it may be safely used or exempts it for investigational use by qualified experts. It is on precisely this basis that the Secretary has, by regulation, restricted the potency of the vitamin folic acid that may be added to a food.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

October 4, 1973

Mr. Walter Ermer
International Health Council
15328 Edolyn Avenue
Cleveland, Ohio 44111

Dear Mr. Ermer:

This is in reply to your letter of August 15, 1973, regarding hypervitaminosis A.

The enclosed reprint from the Federal Register of August 2, 1973 gives our position on the status of vitamin A at page 20723 ff.

To respond to your specific questions, a single dose of over 2,000,000 I.U. of vitamin A can produce an increase in cranial pressure when administered to an adult, and a dose of over 350,000 I.U. can cause the same effect in an infant. Such symptoms are reversible. Continuous daily doses of 4,000-25,000 I.U. per kilogram of body weight for a period of six to fifteen months have been known to produce chronic toxicity.

Information regarding hypervitaminosis A and chronic toxicity due to vitamin A has been gathered from the literature. A copy of a bibliography is enclosed. Texts such as "The Pharmacological Basis of Therapeutics" edited by Louis S. Goodman and Alfred Gilman (4th edition, 1970) provide summaries of knowledge on the subject.

We are not aware of any tests on humans to determine the levels of vitamin A which would produce damage. The implicit hazards preclude such experimentation. Our information on toxic levels has come from reports of accidental ingestion of large amounts and of deliberate, long-term ingestion of high dosages.

Sincerely yours,

Jack Kaye, Chief
Advisory Communications Branch
Bureau of Drugs
BD-49

Enclosures

TRANSCRIPT OF RECORD IN CONSUMERS UNION v. CONSUMER PRODUCT SAFETY COMMISSION

UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

CONSUMERS UNION OF UNITED STATES, INC., Petitioner	)	
v.	)	No. 73-1617
CONSUMER PRODUCT SAFETY COMMISSION, Respondent.	)	

CERTIFIED LIST OF RECORD PURSUANT TO RULE 17(b) OF THE FEDERAL RULES OF APPELLATE PROCEDURE

I hereby certify that the following material listed comprised the record upon which judicial review is sought:

1. Report titled "Position Paper on Grounding of Appliances and Electrical Systems" prepared for the National Commission on Product Safety and dated June 16, 1969.

2. Memorandum of a telephone conversation between Dr. Duan L. Larson and Mr. Dale C. Miller and dated April 17, 1970.

3. Memorandum of a telephone conversation between Colonel Basel Pruitt and Mr. Dale C. Miller and dated April 20, 1970.

4. Memorandum of a meeting prepared by Mr. Richard D. Darby and dated May 6, 1970.

5. Paper titled "Report of Test on Toy Electric Grills" by Samuel D. Toner and dated December 2, 1970.

6. Letter, with attachments, from Aaron Locker to Mack Jensen dated February 5, 1971.

7. Underwriters' Laboratories, Inc., proposed revision of the Standard for Electric Toys (UL696-1966) dated June 29, 1970.

8. Underwriters' Laboratories, Inc., proposed revision of the Standard for Electric Toys (UL696-1966) dated January 11, 1971.

9. Paper titled "TMA Proposed Regs".

10. Memorandum from Donald F. McCaulley to D. C. Miller on the subject of the T.M.A. Proposed Standard-Electrical and Thermal Toys and dated February 18, 1971.

11. Report dated March 18, 1971, containing comments on proposed regulations for thermal and electric toys from the National Bureau of Standards.

12. Draft of Proposed Regulations for Electrical and Electro-Thermal Toys prepared by D. L. Gordon and dated March 18, 1971.

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13. Report titled "Thermal Limitations for Toy Safety" prepared by Yung-Chi Wu and dated March 24, 1971, including reference material.

14. National Bureau or Standards report titled "Toy Metal Casting Sets: Evaluation of Electrical and Thermal Characteristics" dated April 27, 1971, and transmittal letter dated May 3, 1971.

15. Underwriters' Laboratories, Inc., Standard for Safety-Electric Toys (UL696) dated July 1, 1971.

16. Paper titled "Material Properties Criteria for Thermal Safety" by Y. C. Wu and transmittal slip dated December 3, 1971.

17. National Bureau of Standards report titled "Temperature Profiles of Selected Thermal Toys" and transmittal letter dated December 14, 1971.

18. One study entitled "Child Development and Personality", Third Edition, 1969, by Mussen, Conger, and Kagon, published by Harper and Row, Library of Congress catalog Card Number 69-14984.

19. One file labeled "Drafts of Elec. Toy Proposal" consisting of the following:

a. Proposal labeled "First Draft";

b. Proposal labeled "Second Draft" and dated 6-25-71;

BEST COPY AVAILABLE

c. Paper marked "Changes to 7/22/71 draft developed 7/23";

d. Proposal and "Action Memorandum" dated July 23, 1971;

e. Edited proposal and transmittal memoranda variously dated from September 2, 1971, to December 9, 1971; and

f. Revised Proposal and transmittal memorandum dated January 11, 1972.

20. Federal Register notice proposing the banning of certain electrically operated toys and children's articles, 37 Fed. Reg. 1020 et seq.

21. One file labeled "§191&§191(b) - Proposed Classification - Certain Electrically Operated Toys and Other Electrically Operated Children Articles as Banned Hazardous Substances", containing comments collected in the Office of the Hearing Clerk.

22. One file labeled "Drafts of Elec. Toy Order" consisting of the following.

a. Document stamped "Working Draft, Nov. 1972"; and

b. Draft order dated January 18, 1973, with transmittal memorandum dated January 18, 1973, and referenced attachments.

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23. Federal Register order banning certain electrically operated toys and other electrically operated children's articles, 38 Fed. Reg. 6138 et seq.

Samuel M. Hart

SAMUEL M. HART
Acting Secretary
Consumer Product Safety Commission

June 8, 1973

UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

CONSUMERS UNION OF UNITED STATES, INC.,
Petitioner
v.
CONSUMER PRODUCT SAFETY COMMISSION,
Respondent

No. 73-1617

JOINT MOTION TO SUPPLEMENT
CERTIFIED LIST OF RECORD

Petitioner and respondent jointly move this court to supplement the certified list of record in the above-entitled case.

Because of the transfer of authority for the administration of the Federal Hazardous Substances Act, under which the instant case is brought, from the Food and Drug Administration to the Consumer Product Safety Commission, pursuant to 15 U.S.C. 2179(a), all materials which might have been certified as part of the record on appeal were not adequately considered in time for certification of the record by respondent. Therefore, petitioner and respondent jointly move this court to allow the enlargment of the certified record, by addition of the items listed below.

1. Memorandum dated February 8, 1971, from Dale C. Miller, Office of Compliance, to the Director of the Bureau of Product Safety, FDA, re toy standard of the Toy Manufacturers of America.

2. Maximum temperature charts from the draft of UL696, Underwriters' Laboratories Standard for Electric Toys.

3. Draft of proposed regulations, dated March 18, 1971, marked, "D.L. Gordon".

4. Undated draft of proposed regulations.

5. Undated draft of proposed regulations with unidentified pencilled comments.

6. Comments by Sam Hart on proposed regulations (pencilled on yellow legal sheets).

7. Undated carbon copy draft of proposed regulations with unidentified orange pencilled comments.

8. Reprint from Journal of Materials, Vol. 7, No. 4, December 1972, pp. 573-9, of article by Yung-Chi Wu, entitled "Material Properties Criteria for Thermal Safety."

9. Xerox copy of handwritten comments entitled, "Some Individual Comments from Toy Safety Group Members Concerning Standards for Electrically Operated Toys", dated June 21, 1971.

10. Undated draft of proposed regulations with handwritten comment on first page concerning "meeting here next Thursday."

11. Undated draft of maximum acceptable surface temperatures chart from proposed regulations, with penned changes.

12. Draft of proposed preamble and proposed final regulations with pencilled changes.

Respectfully submitted,

Peter H. Schuck

Marsha N. Cohen

Attorneys for Petitioner

Consumers Union of United States, Inc.
1714 Massachusetts Avenue, N.W.
Washington, D.C. 20036

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Consumer Product Safety Commission
U.S. Department of Justice
Washington, D.C. 20530

Michael A. Brown

Paul W. Hallman

Consumer Product Safety Commission
Washington, D.C. 20207

July 20, 1973

So Ordered:

Date: July 27, 1973

A. Daniel Fusaro
Clerk

By: Vincent A. Carlin
Vincent A. Carlin,
Chief Deputy Clerk

A 202 Affidavit of Personal Service of Papers

LUTZ APPELLATE PRINTERS, INC.

UNITED STATES COURT OF APPEALS
SECOND CIRCUIT

THE NATIONAL NUTRITIONAL FOODS ASSOC. and SOLGAR, CO., INC.,

Plaintiffs-Appellants,

against

F. DAVID MATHEWS, et al.,

Defendants-Appellees.

Index No.

Affidavit of Personal Service

STATE OF NEW YORK, COUNTY OF NEW YORK *ss.:*

I, **James A. Steele** *being duly sworn, depose and say that deponent is not a party to the action, is over 18 years of age and resides at* 310 West 146th Street, New York, New York

That on the **10th** *day of* **November** *19* **76** *at* **1 St. Andrews Plaza New York, N.Y.**

deponent served the annexed appendix (vol. 1 & 2 *upon*

Robert B. Fiske, Jr. Attn.: Asst. U.S. Attorney Naomi Reece Buchwald

the **attorney** *in this action by delivering a true copy thereof to said individual personally. Deponent knew the person so served to be the person mentioned and described in said papers as the herein.*

Sworn to before me, this **10th**
day of **November** *19* **76**

Beth A. Hirsh

BETH A. HIRSH
NOTARY PUBLIC, State of New York
No. 41-4623156
Qualified in Queens County
Commission Expires March 30, 1978

James A. Steele

JAMES A. STEELE